0.30mL) in $CH_2Cl_2$ (10mL) at -78 °C was added dropwise a solution of trifluoromethanesulfonic anhydride (2eq, 3.00mmol, 0.50mL). The solution was allowed to warm to room temperature and further stirred for 1 hour. The mixture was quenched with cold water. The aqueous layer was extracted with $CH_2Cl_2$. The combined organic layers were dried over $Na_2SO_4$, filtered and evaporated under reduced pressure to afford the crude product 1-(3-fluorobenzyl)-1,2-dihydro-2-oxopyridin-4-yl trifluoromethanesulfonate as a viscous oil (0.90mmol, 0.41g, 90%). The crude product is used in the next step without further purification.

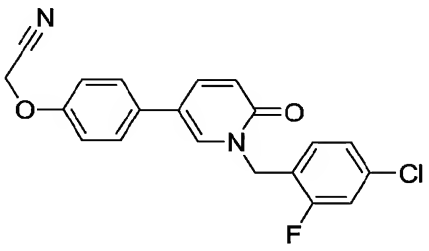
LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 4.34 min; MS *m/z* (CI) $[MH]^+$= 352.

*Step 4 : 1-(3-Fluorobenzyl)-4-(4-methoxyphenyl)pyridin-2(1H)-one*

According to Scheme 13 Method C: The title compound was prepared from 1-(3-fluorobenzyl)-1,2-dihydro-2-oxopyridin-4-yl trifluoromethanesulfonate (1eq, 0.28mmol, 0.10g) and 4-methoxyphenyl boronic acid (1.5eq, 0.43mmol, 65mg) according to the procedure described for Example 1 Step 3. The crude product was purified by flash chromatography on silica gel using cyclohexane/AcOEt 70/30 as eluent to afford the title compound (0.17mmol, 52mg, 59%) was obtained as a white solid.

M.p.: 114°C; LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 4.18 min; MS *m/z* (CI) $[MH]^+$= 310; $^1H$ NMR (500MHz, DMSO-$d^6$) δ 3.80 (s, 3H), 5.11 (s, 2H), 6.62 (dd, J=2.1Hz and 7.2Hz, 1H), 6.66 (d, J=2.0Hz, 1H), 7.02 (d, J=8.9Hz, 2H), 7.09-7.17 (m, 3H), 7.36-7.42 (m, 1H), 7.70 (dd, J=2.1Hz and 6.8Hz, 2H), 7.85 (d, J=7.1Hz, 1H).

**EXAMPLE 20 : 2-(4-(1-(4-Chloro-2-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)-phenoxy)acetonitrile (Final Compound 6-46)**



*Step 1 : 1-(2-Fluoro-4-chlorobenzyl)-5-(4-methoxyphenyl)pyridin-2(1H)-one*

According to Scheme 3 Method A: The title compound was prepared from 1-(4-chloro-2-fluorobenzyl)-5-bromopyridin-2(1*H*)-one (1eq, 16.4mmol, 5.20g, Example 1 Step 2) and 4-methoxyphenylboronic acid (1.5eq, 25.0mmol, 3.80g) according to the procedure described for Example 1 Step 3. The crude product was purified by flash chromatography over silica gel using $CH_2Cl_2$/AcOEt 95/5 to 80/20 as eluent to afford 1-(2-fluoro-4-chlorobenzyl)-5-(4-methoxyphenyl)pyridin-2(1*H*)-one (16.4mmol, 5.64g, 100%) as a white solid.

Rf = 0.29 ($CH_2Cl_2$/AcOEt 90/10); LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 4.58min; MS *m/z* (CI) $[MH]^+$ = 344, 346.

*Step 2 : 1-(4-Chloro-2-fluorobenzyl)-5-(4-hydroxyphenyl)pyridin-2(1H)-one*

According to Scheme 14 Step 1: $BBr_3$ (4eq, 65.6mmol, 6.56mL) was added to a solution of 1-(2-fluoro-4-chlorobenzyl)-5-(4-methoxyphenyl)pyridin-2(1*H*)-one (16.4mmol, 5.64g) in $CH_2Cl_2$ at -50°C. The reaction mixture was stirred 1.5 hour at -40°C, overnight at room temperature then $BBr_3$ (20mL) was added at -30°C and the reaction mixture was stirred 4 hours at room temperature. The reaction mixture was cooled down to -40°C then MeOH (50mL) was added dropwise and the crude mixture was stirred at room temperature. After evaporation, the crude mixture was purified by silica gel chromatography (300g $SiO_2$) using $CH_2Cl_2$/MeOH 95/5 to afford 1-(4-chloro-2-fluorobenzyl)-5-(4-hydroxyphenyl)pyridin-2(1*H*)-one (14.9mmol, 4.80g, 83%) as an orange solid.

M.p.: 207°C; LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 3.67min; MS *m/z* (CI) $[MH]^+$ = 330; $^1H$ NMR (500MHz, $CDCl_3$) δ 5.16 (s, 2H), 6.47 (d, J=9.5Hz, 1H), 6.79 (d, J=8.7Hz, 2H), 7.15-7.20 (m, 1H), 7.25 (dd, J=2.1Hz and 8.7Hz, 1H), 7.34 (d, J=6.6Hz, 2H), 7.45 (dd, J=2.1Hz and 10.1Hz, 1H), 7.77 (dd, J=2.7Hz and 9.5Hz, 1H), 8.03 (d, J=2.7Hz, 1H), 9.51 (s, 1H).

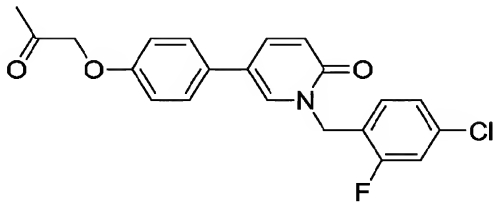
*Step 3 : 2-(4-(1-(4-Chloro-2-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)phenoxy)-acetonitrile*

According to Scheme 14 Method A: A suspension of 1-(4-chloro-2-fluorobenzyl)-5-(4-hydroxyphenyl)pyridin-2(1*H*)-one (1eq, 1.21mmol, 0.40g), $K_2CO_3$ (10eq, 12.1mmol,

1.68g) and 2-bromoacetonitrile (1eq, 1.21mmol, 0.15g) in acetonitrile (10mL) was heated in a microwave at 180°C during 5 min. The reaction mixture was filtered, the filtrate was concentrated and the resulting crude residue was dissolved in $CH_2Cl_2$. The organic phase was washed with water, dried over $MgSO_4$, filtered and evaporated. The crude oil was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 25g $SiO_2$) using $CH_2Cl_2$/MeOH 98/2 as eluent followed by trituration in acetonitrile to afford 2-(4-(1-(4-chloro-2-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)phenoxy)acetonitrile (0.51mmol, 0.19g, 42%) as a white solid.

M.p.: 160°C; LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 4.20min; MS *m/z* (CI) $[MH]^+$= 369, 371; $^1H$ NMR (300MHz, $CDCl_3$) δ 5.19 (s, 2H), 5.20 (s, 2H), 6.52 (d, J=9.5Hz, 1H), 7.11-7.16 (m, 2H), 7.18-7.23 (m, 1H), 7.27 (dd, J=2.0Hz and 8.4Hz, 1H), 7.46 (dd, J=2.0Hz and 10.1Hz, 1H), 7.55-7.60 (m, 2H), 7.86 (dd, J=2.7Hz and 9.5Hz, 1H), 8.16 (d, J=2.7Hz, 1H).

**EXAMPLE 21 : 1-(4-Chloro-2-fluorobenzyl)-5-(4-(2-oxopropoxy)phenyl)pyridin-2(1*H*)-one (Final Compound 6-40)**

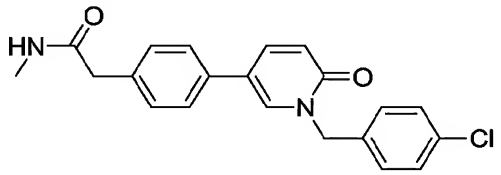



According to Scheme 14 Method A: A suspension of 1-(4-chloro-2-fluorobenzyl)-5-(4-hydroxyphenyl)pyridin-2(1*H*)-one (1eq, 0.61mmol, 0.20g, Example 20 Step 2), $K_2CO_3$ (10eq, 6.10mmol, 0.84g) and chloroacetone (4eq, 2.43mmol, 0.20mL) in THF (10mL) was heated in a microwave at 110°C during 30 min. After filtration and evaporation, the resulting crude oil was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 25g $SiO_2$) using $CH_2Cl_2$/AcOEt 80/20 then was washed with $Et_2O$ and was dried to afford 1-(4-chloro-2-fluorobenzyl)-5-(4-(2-oxopropoxy)phenyl)pyridin-2(1*H*)-one (0.12mmol, 46mg, 20%) as a white solid.

M. p.: 127°C; LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 4.02min; MS *m/z* (CI) $[MH]^+$= 386, 388; $^1H$ NMR (300MHz, $CDCl_3$) δ 2.16 (s, 3H), 4.83 (s, 2H), 5.18 (s, 2H), 6.50 (d, J=9.3Hz, 1H), 6.93-7.02 (m, 2H), 7.15-7.24 (m, 1H), 7.27 (dd, J=2.1Hz

and 8.7Hz, 1H), 7.42-7.51 (3H), 7.83 (dd, J=2.4Hz and 9.3Hz, 1H), 8.11 (d, J=2.4Hz, 1H).

**EXAMPLE 22: 2-(4-(1-(4-Chlorobenzyl)-1,6-dihydro-6-oxopyridin-3-yl)phenyl)-*N*-methylacetamide (Final Compound 2-44)**



*Step 1 : 2-(4-(1-(4-Chlorobenzyl)-1,6-dihydro-6-oxopyridin-3-yl)phenyl)acetic acid*

According to Scheme 3 Method A: The title compound was prepared according to Example 2 Step 2, from 1-(4-chlorobenzyl)-5-bromopyridin-2(1*H*)-one (1eq, 0.67mmol, 0.20g, Example 2 Step 1) and 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetic acid (1.5eq, 1.00mmol, 0.26g). Reaction conditions: 4.5 hours at 90°C. The reaction mixture was made acidic then extracted with AcOEt. The organic layer was washed with brine, dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by chromatography over silicagel (AIT Flashsmart prepacked column 25g $SiO_2$, AcOEt/MeOH 95/5), yielding the title compound (0.24g, 100%) as a white solid.

LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 3.53min; MS *m/z* (CI) $[MH]^+$= 354, 356.

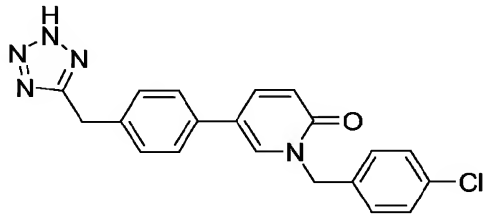
*Step 2 : 2-(4-(1-(4-Chlorobenzyl)-1,6-dihydro-6-oxopyridin-3-yl)phenyl)-N-methyl acetamide*

Scheme 15 Method B: The title compound was prepared according to Example 14 Step 3, from 2-(4-(1-(4-chlorobenzyl)-1,6-dihydro-6-oxopyridin-3-yl)phenyl)acetic acid (1eq, 0.10mmol, 50mg) and methylamine (2M in MeOH, 0.10mmol, 0.07mL), then purified by chromatography over silicagel (AIT Flashsmart prepacked column 10g $SiO_2$, $CH_2Cl_2$/AcOEt 50/50), yielding the title compound (0.07mmol, 34mg, 66%) as a white solid.

M.p.: 183°C; LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 3.32min; MS *m/z* (CI) $[MH]^+$= 367, 369; $^1H$ NMR (300 MHz, DMSO-$d^6$) δ 2.56 (d, J=4.6Hz, 3H), 3.36

(s, 2H), 5.15 (s, 2H), 6.52 (d, J=9.5Hz, 1H), 7.29 (d, J=8.2Hz, 2H), 7.33-7.45 (4H), 7.49 (d, J=8.2Hz, 2H), 7.83 (dd, J= J=2.6Hz, 9.45Hz, 1H), 7.92-8.01 (m, 1H), 8.24 (d, J=2.6Hz, 1H).

**EXAMPLE 23 : 5-(4-((2*H*-Tetrazol-5-yl)methyl)phenyl)-1-(4-chlorobenzyl) pyridin-2(1*H*)-one (Final Compound 2-51)**



*Step 1 : 2-(4-(1-(4-Chlorobenzyl)-1,6-dihydro-6-oxopyridin-3-yl)phenyl)acetonitrile*

According to Scheme 3 Method A: The title compound was synthesized as described in Example 2 Step 2 using 4-(cyanomethyl)phenyl boronic acid (1.5eq, 0.50mmol, 80.9mg) and 1-(4-chlorobenzyl)-5-bromopyridin-2(1*H*)-one (1eq, 0.33mmol, 0.10g, Example 2 Step 1) as substrates. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 25g $SiO_2$) using $CH_2Cl_2$/AcOEt to afford 2-(4-(1-(4-chlorobenzyl)-1,6-dihydro-6-oxopyridin-3-yl)phenyl)acetonitrile as a yellow solid (0.33mmol, 110mg, 98%).

M.p.: 172°C; LC (XTerra RP18, 3.5µm, 3.0x50mm Column): RT = 4.18 min, MS *m/z* (CI) $[MH]^+$= 335, 337.

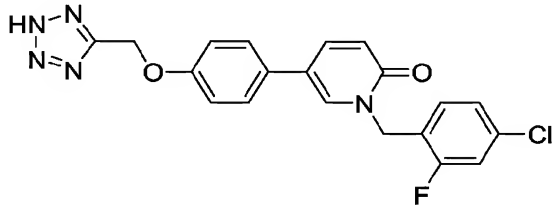
*Step 2 : 5-(4-((2H-Tetrazol-5-yl)methyl)phenyl)-1-(4-chlorobenzyl)pyridin-2(1H)-one*

According to Scheme 15 Method D: 2-(4-(1-(4-Chlorobenzyl)-1,6-dihydro-6-oxopyridin-3-yl)phenyl)acetonitrile (1eq, 0.24mmol, 0.08g) was heated at 110°C under nitrogen overnight with dibutyltin oxide (0.22eq, 0.05mmol, 0.01g) and azidotrimethylsilane (6.0eq, 1.43mmol, 0.19mL) in toluene (4mL). The suspension was filtered and the filtrate concentrated under vacuo. The crude product was purified by chromatography on silica gel using MeOH/AcOEt 20/80 as eluent and recristallised in diisopropyl ether to afford the title compound as a white solid (0.09mmol, 35mg, 39%).

M.p.: 231°C; LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 3.56 min; MS *m/z* (CI) $[MH]^+$= 376, 378; $^1H$ NMR (500MHz, DMSO-$d^6$) δ 3.99 (s, 2H), 5.13 (s, 2H),

6.48 (d, J= 9.5Hz, 1H), 7.25 (d, J=8.4Hz, 2H), 7.35-7.40 (4H), 7.42 (d, J=8.4Hz, 2H), 7.80 (dd, J=2.7Hz and 9.5Hz, 1H), 8.21 (d, J=2.5Hz, 1H).

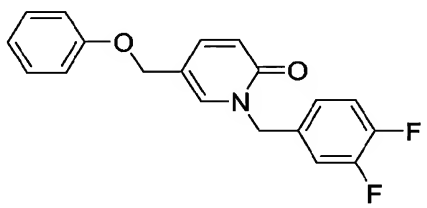
**EXAMPLE 24 : 5-(4-((2*H*-Tetrazol-5-yl)methoxy)phenyl)-1-(4-chloro-2-fluoro benzyl)pyridin-2(1*H*)-one (Final Compound 6-65)**



According to Scheme 15 Method D: The title compound was prepared from 2-(4-(1-(4-chloro-2-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)phenoxy)acetonitrile (1eq, 0.35mmol, 0.13g, Example 20 Step 3) according to the procedure described for Example 23 Step 2. The crude product was purified by silica gel chromatography (AIT Flashsmart prepacked column 10g $SiO_2$) using $CH_2Cl_2$/MeOH 95/5 as eluent followed by trituration in $Et_2O$ to afford 5-(4-((2*H*-tetrazol-5-yl)methoxy)phenyl)-1-(4-chloro-2-fluorobenzyl)pyridin-2(1*H*)-one (85µmol, 35mg, 24%) as a white solid.

M.p.: 197°C; LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 3.57min; MS *m/z* (CI) $[MH]^+$= 412, 414; $^1H$ NMR (300MHz, $CDCl_3$) δ 3.00-3.60 (br. s, 1H), 5.18 (s, 2H), 5.35 (s, 2H), 6.50 (d, J=9.5Hz, 1H), 7.11-7.17 (m, 2H), 7.18-7.23 (m, 1H), 7.27 (dd, J=2.0Hz and 8.4Hz, 1H), 7.45 (dd, J=2.0Hz and 10.2Hz, 1H), 7.47-7.60 (m, 2H), 7.84 (dd, J=2.7Hz and 9.5Hz, 1H), 8.13 (d, J=2.7Hz, 1H).

**EXAMPLE 25 : 1-(3,4-Difluorobenzyl)-5-(phenoxymethyl)pyridin-2(1*H*)-one (Final Compound 16-03)**



*Step 1 : (6-Methoxypyridin-3-yl)methanol*

According to Scheme 16 Method A: A solution of 6-methoxynicotinaldehyde (1eq, 2.19mmol, 0.30g) and $LiAlH_4$ (0.5eq, 1.05mmol, 0.04g) in THF (10mL) was stirred for 30 min. at 0°C and overnight at room temperature. After the addition of AcOEt, the reaction mixture was diluted with water. The organic layer was washed with saturated $NH_4Cl$ solution, dried over $Na_2SO_4$, filtered and evaporated. The resulting crude residue was purified by silica gel chromatography (AIT Flashsmart prepacked column 25g $SiO_2$) using $CH_2Cl_2$/AcOEt 80/20 to afford (6-methoxypyridin-3-yl)methanol (1.80mmol, 0.26g, 90%) as a pale oil.

LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 1.86min; MS *m/z* (CI) $[MH]^+$= 140.

*Step 2 : 2-Methoxy-5-(phenoxymethyl)pyridine*

According to Scheme 16 Method A: Phenol (1.5eq, 2.80mmol, 0.26g), $PPh_3$ (2eq, 3.70mmol, 1.20g) and DEAD (2eq, 3.70mmol, 1.60g) were added to a solution of (6-methoxypyridin-3-yl)methanol (1eq, 1.87mmol, 0.26g) in THF (6mL). The reaction mixture was stirred overnight at room temperature. After evaporation of the solvent, the reaction mixture was diluted with water. The organic layer was washed with saturated $NaHCO_3$ solution, dried over $Na_2SO_4$, filtered and evaporated. The resulting crude residue was purified by silica gel chromatography (AIT Flashsmart prepacked column 25g $SiO_2$) using cyclohexane/AcOEt 85/15 to afford 2-methoxy-5-(phenoxymethyl)pyridine (0.93mmol, 0.20g, 49%) as a pale oil.

LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 4.46min; MS *m/z* (CI) $[MH]^+$= 216.

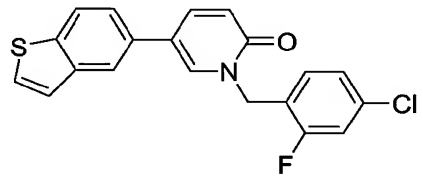
*Step 3 : 1-(3,4-Difluorobenzyl)-5-(phenoxymethyl)pyridin-2(1H)-one*

According to Scheme 16 Method A: The title compound was prepared from 2-methoxy-5-(phenoxymethyl)pyridine (1eq, 0.46mmol, 0.10g) and 4-(bromomethyl)-1,2-difluorobenzene (3eq, 1.39mmol, 0.18mL) according to the procedure described for Example 1 Step 2. Reaction conditions: under reflux for 3 days in DMF (5mL). The crude oil was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 25g $SiO_2$) using $CH_2Cl_2$/AcOEt 90/10 followed by recrystallization

in diisopropyl ether to afford 1-(3,4-difluorobenzyl)-5-(phenoxymethyl)pyridin-2(1*H*)-one (0.14mmol, 0.04g, 29%) as a white solid.

M.p.: 89°C; LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 4.29min; MS *m/z* (CI) $[MH]^+$= 328; $^1H$ NMR (500MHz, DMSO-$d^6$) δ 4.80 (s, 2H), 5.06 (s, 2H), 6.45 (d, J=9.3Hz, 1H), 6.91-6.96 (m, 1H), 6.96-6.99 (m, 2H), 7.12-7.17 (m, 1H), 7.25-7.30 (m, 2H), 7.36-7.43 (m, 2H), 7.53 (dd, J=2.5Hz and 9.3Hz, 1H), 7.99 (d, J=2.3Hz, 1H).

**EXAMPLE 26 : 1-(4-Chloro-2-fluorobenzyl)-5-(benzo[*b*]thiophen-5-yl)pyridin-2(1*H*)-one (Final Compound 6-69)**




*Step 1 : 1-(4-Chloro-2-fluorobenzyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one*

According to Scheme 17 Step 1: To a solution of 1-(4-chloro-2-fluorobenzyl)-5-bromopyridin-2(1*H*)-one (1eq, 1.26mmol, 0.40g, Example 1 Step 2) in degazed dioxane (20mL) was added under nitrogen 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1.3eq, 1.64mmol, 0.42g), $PdCl_2(dppf)_2$ (0.03eq, 38µmol, 28mg), dppf (0.06eq, 76µmol, 42mg) and KOAc (3eq, 3.79mmol, 0.37g). The reaction mixture was stirred at 80°C for 4 hours, was quenched with water and the aqueous phase was extracted with AcOEt. The organic phase was dried over $Na_2SO_4$, filtered and concentrated. The crude product was purified by silica gel chromatography (AIT Flashsmart prepacked column 25g $SiO_2$) using $CH_2Cl_2$/AcOEt 90/10 as eluent to afford 1-(4-chloro-2-fluorobenzyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1*H*)-one (0.74mmol, 0.27g, 59%) as a pale oil.

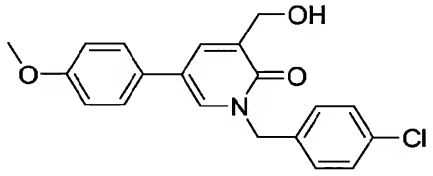
LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 3.03min; MS *m/z* (CI) $[MH]^+$= 364, 366.

*Step 2 : 1-(4-Chloro-2-fluorobenzyl)-5-(benzo[b]thiophen-5-yl)pyridin-2(1H)-one*

According to Scheme 17 Step 2: The title compound was prepared from 1-(4-chloro-2-fluorobenzyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1*H*)-one (1eq, 1.26mmol, 0.40g) and 5-bromobenzo[*b*]thiophene (1.5eq, 0.29mmol, 0.06g) according to the procedure described for Example 1 Step 2. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 25g $SiO_2$) using $CH_2Cl_2$/AcOEt 90/10 and by crystallization with diisopropyl ether/pentane to afford the title compound (17µmol, 6.4mg, 9%) as a white solid.

M.p.: 110°C; LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 5.03min; MS *m/z* (CI) $[MH]^+$= 370, 372; $^1H$ NMR (500MHz, DMSO-$d^6$) δ 5.21 (s, 2H), 6.55 (d, J=9.5Hz, 1H), 7.19-7.24 (m, 1H), 7.26-7.30 (m, 1H), 7.43-7.49 (m, 2H), 7.57 (dd, J=1.8Hz and 8.6Hz, 1H), 7.80 (d, J=5.4Hz, 1H), 7.95 (dd, J=2.7Hz and 9.4Hz, 1H), 8.05 (d, J=8.4Hz, 1H), 8.07 (d, J=1.6Hz, 1H), 8.28 (d, J=2.3Hz, 1H).

**Example 27 : 1-(4-Chlorobenzyl)-3-(hydroxymethyl)-5-(4-methoxyphenyl)pyridin-2(1*H*)-one (Final Compound 9-08)**




*Step 1 : Methyl 1-(4-chlorobenzyl)-5-bromo-2-oxo-1,2-dihydropyridine-3-carboxylate*

According to Scheme 1 Step 2: The title compound was prepared from methyl 5-bromo-2-oxo-1,2-dihydropyridine-3-carboxylate (1eq, 10.0mmol, 3.00g) and 1-(bromomethyl)-4-chlorobenzene (1.5eq, 20.0mmol, 4.00g) according to the procedure described for Example 1 Step 2. Reaction conditions: 3 hours at 50°C in THF/DMF (2:1, 300mL). The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepacked 130g column $SiO_2$) using $CH_2Cl_2$/AcOEt 85/15 as the eluent and recrystallized from $Et_2O$ to afford the title compound (9.00mmol, 4.17g, 90%) as a white solid.

LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 4.05min; MS *m/z* (CI) $[MH]^+$= 357, 359.

*Step 2 : Methyl 1-(4-chlorobenzyl)-5-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate*

According to Scheme 3 Method A: The title compound was prepared from methyl 1-(4-chlorobenzyl)-5-bromo-2-oxo-1,2-dihydropyridine-3-carboxylate (1eq, 7.00mmol, 2.50g) and 4-methoxyphenyl boronic acid (1.5eq, 11.0mmol, 1.60g) according to the procedure described for Example 1 Step 3. Reaction conditions: 4 hours at 80°C. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 80g $SiO_2$) using $CH_2Cl_2$/AcOEt 80/20 and by recrystallization with $Et_2O$/pentane to afford methyl 1-(4-chlorobenzyl)-5-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (5.74mmol, 2.22g, 82%) as a beige solid.

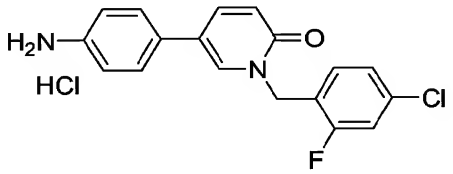
LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 4.38min; MS *m/z* (CI) $[MH]^+$= 384, 386.

*Step 3 : 1-(4-Chlorobenzyl)-3-(hydroxymethyl)-5-(4-methoxyphenyl)pyridin-2(1H)-one*

According to Scheme 18: To a solution of methyl 1-(4-chlorobenzyl)-5-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (1eq, 0.52mmol, 0.20g) in $Et_2O$ (7mL) at -78°C was added DIBAL (3eq, 1.60mmol, 1.11g). The reaction was stirred at -78°C for 30 minutes and 0°C for 1 hour. The reaction was then allowed to warm to room temperature and quenched with saturated aqueous $NH_4Cl$ solution. The aqueous phase was extracted 3 times with AcOEt and the combined organic fractions were washed twice with water, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepacked 50g column $SiO_2$) using $CH_2Cl_2$/AcOEt 80/20 as eluent which was then recrystallized from pentane/$Et_2O$ to afford the title compound (0.04mmol, 16.0mg, 9%) as a beige solid.

M.p.: 128°C; LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 3.98min; MS *m/z* (CI) $[MH]^+$= 356, 358; $^1H$ NMR (300MHz, DMSO-$d^6$) δ 3.77 (s, 3H), 4.37 (d, J=5.8Hz, 2H), 5.12-5.19 (3H), 7.00 (d, J=8.9Hz, 2H), 7.35-7.43 (m, 4H), 7.44-7.52 (m, 2H), 7.72-7.76 (m, 1H), 8.07-8.10 (m, 1H).

**EXAMPLE 28 : 1-(4-Chloro-2-fluorobenzyl)-5-(4-aminophenyl)pyridin-2(1*H*)-one hydrochloride (Final Compound 6-23)**




*Step 1 : tert-Butyl 4-(1-(4-chloro-2-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl) phenylcarbamate*

According to Scheme 19 Step 1: The title compound was prepared from 1-(4-chloro-2-fluorobenzyl)-5-bromopyridin-2(1*H*)-one (1eq, 2.81mmol, 0.89g, Example 1 Step 2) and 4-(*tert*-butoxycarbonyl)aminophenylboronic acid (1.5eq, 4.20mmol, 1.00g) according to the procedure described for Example 1 Step 3. Reaction conditions: 2 hours at 80°C. The crude product was purified by silica gel chromatography (AIT Flashsmart prepacked column 50g $SiO_2$, $CH_2Cl_2$/AcOEt 90/10). The resulting brown solid was washed twice with acetonitrile to afford *tert*-butyl 4-(1-(4-chloro-2-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)phenylcarbamate (2.11mmol, 0.90g, 75%) as a beige solid.

M.p.: 208°C; LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 4.82min; MS *m/z* (CI) $[MH]^+$= 429, 431.

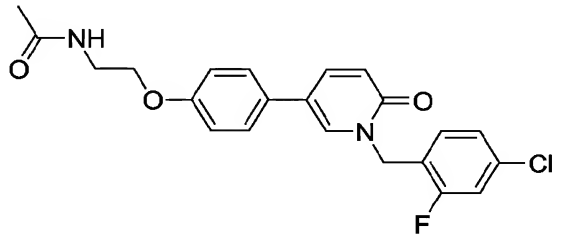
*Step 2 : 1-(4-Chloro-2-fluorobenzyl)-5-(4-aminophenyl)pyridin-2(1H)-one hydrochloride*

According to Scheme 19 Step 2: HCl/dioxane (10eq, 4M, 5.00mL) was added to a solution of *tert*-butyl 4-(1-(4-chloro-2-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)phenylcarbamate (1eq, 2.00mmol, 1.00g) in MeOH (20mL) at 0°C. The reaction was stirred for 2 days at 80°C, then the solvent was concentrated and $Et_2O$ was added. The solid was filtered and dried to yield 1-(4-chloro-2-fluorobenzyl)-5-(4-aminophenyl)pyridin-2(1*H*)-one hydrochloride (1.78mmol, 0.76g, 89%) as a beige solid.

M.p.: 266°C; LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 3.18min; MS *m/z* (CI) $[MH]^+$= 329, 331; $^1H$ NMR (300MHz, DMSO-$d^6$) δ 3.10-3.70 (br s, 3H), 5.19 (s,

2H), 6.53 (d, J=9.5Hz, 1H), 7.16-7.24 (m, 1H), 7.24-7.37 (3H), 7.46 (dd, J=1.8Hz and 10.2Hz, 1H), 7.63 (dd, J=8.2Hz, 2H), 7.87 (dd, J=2.6Hz and 9.5Hz, 1H), 8.23 (s, 1H).

**EXAMPLE 29 : *N*-(2-(4-(1-(4-Chloro-2-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)phenoxy)ethyl)acetamide (Final Compound 6-53)**



*Step 1 : tert-Butyl 2-(4-(1-(4-chloro-2-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)phenoxy)ethylcarbamate*

The title compound was prepared from 1-(4-chloro-2-fluorobenzyl)-5-(4-hydroxyphenyl)pyridin-2(1*H*)-one (1eq, 0.60mmol, 0.20g, Example 20 Step 2) and *tert*-butyl 2-hydroxyethylcarbamate (1.5eq, 0.90mmol, 0.10g) according to the procedure described for Example 25 Step 2. The crude product was purified by crystallization in pentane/$Et_2O$ followed by silica gel chromatography (AIT Flashsmart prepacked column 25g $SiO_2$, $CH_2Cl_2$/AcOEt 80/20) to afford *tert*-butyl 2-(4-(1-(4-chloro-2-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)phenoxy)ethylcarbamate (0.40mmol, 0.19g, 66%) as a yellow oil.

LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 4.73min; MS *m/z* (CI) $[MH]^+$= 473, 475.

*Step 2 : 1-(4-Chloro-2-fluorobenzyl)-5-(4-(2-aminoethoxy)phenyl)pyridin-2(1H)-one*

According to Scheme 19 Step 2: The title compound was prepared from *tert*-butyl 2-(4-(1-(4-chloro-2-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)phenoxy)ethylcarbamate (1eq, 0.40mmol, 0.19g) according to the procedure described for Example 28 Step 2. Reaction conditions: room temperature overnight. After trituration with $Et_2O$, 1-(4-chloro-2-fluorobenzyl)-5-(4-(2-aminoethoxy)phenyl)pyridin-2(1*H*)-one (0.40mmol, 0.16g, 100%) was obtained as a white solid.

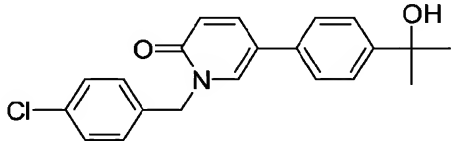
M.p.: 226°C; LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 2.63min; MS *m/z* (CI) $[MH]^+$= 373, 375.

*Step 3 : N-(2-(4-(1-(4-Chloro-2-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)phenoxy) ethyl)acetamide*

According to Scheme 19 Step 3: To a solution of 1-(4-chloro-2-fluorobenzyl)-5-(4-(2-aminoethoxy)phenyl)pyridin-2(1*H*)-one (1eq, 0.18mmol, 0.07g) in $CH_2Cl_2$ (5mL) at 0°C were added $Et_3N$ (6eq, 1.10mmol, 0.15mL) and 30 min. later acetyl chloride (1.5eq, 0.27mmol, 19µL) and. The reaction mixture was stirred 1 hour at room temperature. The reaction mixture was quenched with water and extracted with $CH_2Cl_2$. The organic phase was dried over $Na_2SO_4$, filtered and evaporated. The crude product was purified by silica gel chromatography (AIT Flashsmart prepacked column 25g $SiO_2$, $CH_2Cl_2$/AcOEt 70/30) to afford *N*-(2-(4-(1-(4-chloro-2-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)phenoxy)ethyl)acetamide (0.08mmol, 0.04g, 47%) as a white solid.

M.p.: 153°C; LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 3.51min; MS *m/z* (CI) $[MH]^+$=415, 417; $^1H$ NMR (300MHz, DMSO-$d^6$) δ 3.16 (s, 3H), 3.99 (t, J=5.6Hz, 2H), 5.18 (s, 2H), 5.75 (s, 1H), 6.51 (d, J=9.5Hz, 1H), 7.00 (d, J=8.7Hz, 2H), 7.15-7.23 (m, 1H), 7.23-7.29 (m, 1H), 7.43-7.53 (m, 3H), 7.84 (dd, J=2.8Hz and 9.5Hz, 1H), 8.09-8.20 (m, 1H).

**EXAPLE 30 : 1-(4-Chlorobenzyl)-5-(4-(2-hydroxypropan-2-yl)phenyl)pyridin-2(1*H*)-one (Final Compound 2-15)**




*Step 1 : 1-(4-Chlorobenzyl)-5-(4-acetylphenyl)pyridin-2(1H)-one*

According to Scheme 3 Method A: The title compound was prepared from 1-(4-chlorobenzyl)-5-bromopyridin-2(1*H*)-one (Example 2 Step 1) and 4-acetylphenylboronic acid according to the procedure described for Example 2 Step 2. Reaction conditions: 4 hours at 80°C. The crude product was purified by silica gel

chromatography (AIT Flashsmart prepacked column 25g $SiO_2$) using $CH_2Cl_2$/AcOEt 50/50 as eluent to afford 1-(4-chlorobenzyl)-5-(4-acetylphenyl)pyridin-2(1*H*)-one (0.29mmol, 0.10g, 86%) as a yellow solid.

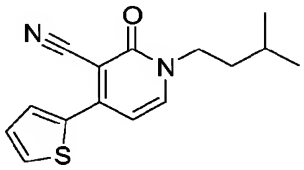
M.p.: 162°C; LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 4.21min; MS *m/z* (CI) $[MH]^+$= 338, 340; $^1H$ NMR (500MHz, DMSO-$d^6$) δ 2.58 (s, 3H), 5.17 (s, 2H), 6.55 (d, J=9.4Hz, 1H), 7.37-7.42 (4H), 7.74 (d, J=2.6Hz, 2H), 7.95 (dd, J=2.6Hz and 9.4Hz, 1H), 7.99 (d, J=8.6Hz, 2H), 8.45 (d, J=2.6Hz, 1H).

*Step 2 : 1-(4-Chlorobenzyl)-5-(4-(2-hydroxypropan-2-yl)phenyl)pyridin-2(1H)-one*

According to Scheme 20: To a solution of 1-(4-chlorobenzyl)-5-(4-acetylphenyl)pyridin-2(1*H*)-one (1eq, 0.20mmol, 80mg) in THF (5mL) at -50°C was added a solution of methyl magnesium bromide (3M, 1.3eq, 0.30mmol, 0.04g) and the reaction stirred at -50°C for 1 hour. The reaction was quenched at -78°C with saturated aqueous $NH_4Cl$. The reaction was allowed to warm to room temperature and diluted with AcOEt and the organic phase extracted (x3). The combined organic fractions were dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 25g $SiO_2$) using $CH_2Cl_2$/AcOEt 80/20 and was recrystallized from pentane/$Et_2O$ to afford 1-(4-chlorobenzyl)-5-(4-(2-hydroxypropan-2-yl)phenyl)pyridin-2(1*H*)-one (0.08mmol, 30mg, 36%) as a white solid.

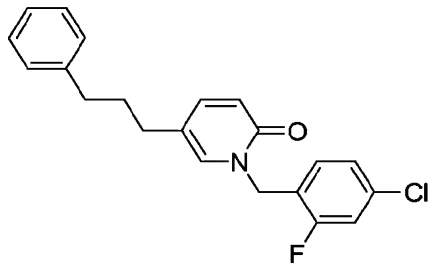
M.p.: 157°C. LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 3.86min; MS *m/z* (CI) $[MH]^+$= 354, 356. $^1H$ NMR (300MHz, DMSO-$d^6$) δ 1.42 (s, 6H), 5.05 (s, 1H), 5.15 (s, 2H), 6.52 (d, J=9.7Hz, 1H), 7.32-7.43 (m, 4H), 7.43-7.52 (m, 3H), 7.84 (dd, J=1.8Hz, 9.5Hz, 1H), 8.22 (d, J=1.8Hz, 1H).

**EXAMPLE 31 : 1,2-Dihydro-1-isopentyl-2-oxo-4-(thiophen-2-yl)pyridine-3-carbonitrile (Final Compound 10-28)**



According to Scheme 21: The title compound was prepared according to Example 1 Step 2 from 1,2-dihydro-2-oxo-4-(thiophen-2-yl)pyridine-3-carbonitrile (1eq, 0.50mmol, 0.10g) and 1-bromo-3-methylbutane (1.5eq, 0.70mmol, 0.10g). Reaction conditions: 17 hours at 60°C in acetonitrile (10mL). The crude product was purified by chromatography over silicagel (AIT Flashsmart prepacked column $SiO_2$, cyclohexane/AcOEt 80/20) and recrystallized in pentane/$Et_2O$ yielding the title compound (88mg, 0.30mmol, 65%) as a yellow solid. M.p.: 123°C; LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 4.29min; MS *m/z* (CI) $[MH]^+$= 273; $^1H$ NMR (300 MHz, DMSO-$d^6$) δ 0.92 (d, J=5.6Hz, 6H), 1.48-1.63 (m, 3H), 3.90-4.02 (m, 2H), 6.72 (d, J=7.2Hz, 1H), 7.32 (d, J=8.4Hz, 1H), 7.96-8.04 (m, 2H), 8.08 (d, J=7.2Hz, 1H).

**EXAMPLE 32 : 1-(4-Chloro-2-fluorobenzyl)-5-(3-phenylpropyl)pyridin-2(1*H*)-one (Final Compound 7-08)**




*Step 1 : 2-Methoxy-5-(3-phenylpropyl)pyridine*

According to Scheme 22 Method A: To a solution of 5-bromo-2-methoxypyridine (1eq, 2.70mmol, 0.50g) in THF (4.4mL) at -78°C under nitrogen was added dropwise n-butyl lithium (1eq, 2.5M in hexanes, 2.70mmol, 1.10mL). The reaction mixture was stirred at -78°C for 30 min. and 1-(3-bromopropyl)benzene (1eq, 2.70mmol, 0.40mL) in solution in THF (1mL) was added dropwise. The reaction mixture was stirred at -78°C for 30 min. and then allowed to warm to room temperature for 1 hour. The reaction was quenched at 0°C with water and extracted with $Et_2O$. The organic phase was dried over $Na_2SO_4$, filtered and solvent was removed under reduced pressure leaving an orange oil. This residue was purified by flash chromatography over silicagel (AIT Flashsmart prepacked column $SiO_2$, cyclohexane/AcOEt 97.5/2.5), yielding the title compound (0.46mmol, 0.10g, 17%) as a colorless semi-solid.

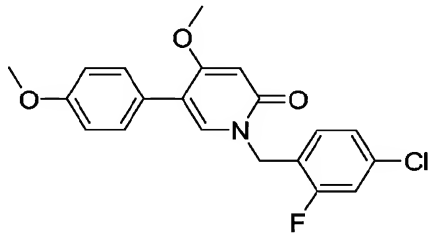
LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 5.08min; MS *m/z* (CI) $[MH]^+$= 228.

*Step 2 : 1-(4-Chloro-2-fluorobenzyl)-5-(3-phenylpropyl)pyridin-2(1H)-one*

According to Scheme 22 Step 2: The title compound was prepared according to Example 6 Step 2, from 2-methoxy-5-(3-phenylpropyl)pyridine (1eq, 0.44mmol, 0.10g) and 1-(bromomethyl)-4-chloro-2-fluorobenzene (2eq, 0.88mmol, 0.20g). Reaction conditions: overnight at 90°C. The residue was purified by flash chromatography over silicagel (AIT Flashsmart prepacked column $SiO_2$, cyclohexane/AcOEt 70/30) yielding the title compound (75mg, 0.21mmol, 48%) as a yellow oil.

LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 5.07min; MS *m/z* (CI) $[MH]^+$= 356, 358; $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.76-1.93 (m, 2H), 2.30-2.46 (m, 2H), 2.52-2.70 (m, 2H), 5.09 (s, 2H), 6.54 (d, J=9.2Hz, 1H), 7.04-7.35 (9H), 7.35-7.50 (m, 1H).

**EXAMPLE 33 : 1-(4-Chloro-2-fluorobenzyl)-4-methoxy-5-(4-methoxyphenyl) pyridin-2(1*H*)-one (Final Compound 9-18)**




*Step 1 : 2,4-Dimethoxypyridine*

According to Scheme 23 Step 1: To a solution of sodium methoxide (30% in MeOH, 2eq, 35mmol) was added 2-chloro-4-methoxypyridine (1eq, 17.0mmol, 2.50g). The reaction was refluxed overnight. The reaction was allowed to cool, poured onto water (10mL) and extracted with $CH_2Cl_2$ (3x10mL). The combined organic fractions were dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to afford 2,4-dimethoxypyridine (10.1mmol, 1.40g, 58%) as a colorless oil. The crude product was reacted on.

LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 1.40min; MS *m/z* (CI) $[MH]^+$= 140.

*Step 2 : 5-Bromo-2,4-dimethoxypyridine*

According to Scheme 23 Step 2: To a solution of KOH (0.5eq, 0.8mmol, 40mg) in water (75mL) was added 2,4-dimethoxypyridine (1eq, 2.00mmol, 0.21g) followed by the dropwise addition of $Br_2$ (1eq, 2.00mmol, 0.20g) in 1M aqueous KBr solution (75mL). The reaction was stirred at room temperature for 5 hours and then poured onto water (10mL) and extracted with $CH_2Cl_2$ (3x10mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford 5-bromo-2,4-dimethoxypyridine (1.40mmol, 0.30g, 70%) as a colorless oil. The crude product was reacted on.

LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 3.92min; MS *m/z* (CI) $[MH]^+$= 219, 221.

*Step 3 : 2,4-Dimethoxy-5-(4-methoxyphenyl)pyridine*

According to Scheme 23 Step 3: The title compound was prepared from 5-bromo-2,4-dimethoxypyridine (1eq, 1.40mmol, 0.30g) and 4-methoxyphenylboronic acid (1.5eq, 2.10mmol, 0.32g) according to the procedure described for Example 1 Step 3. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 25g $SiO_2$) using $CH_2Cl_2$/MeOH 98/2 to afford 2,4-dimethoxy-5-(4-methoxyphenyl)pyridine (1.39mmol, 0.34g, 99%) as a brown oil.

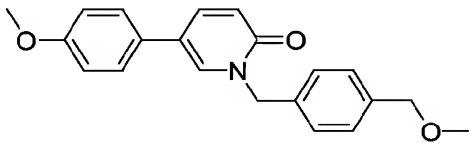
LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 3.85min; MS *m/z* (CI) $[MH]^+$= 246, 248.

*Step 4 : 1-(4-Chloro-2-fluorobenzyl)-4-methoxy-5-(4-methoxyphenyl)pyridin-2(1H)-one*

According to Scheme 23 Step 4: The title compound was prepared from 2,4-dimethoxy-5-(4-methoxyphenyl)pyridine (1eq, 0.20mmol, 0.05g) and 4-chlorobenzyl-2-fluorobenzyl bromide (1.5eq, 0.30mmol, 68mg) according to the procedure described for Example 6 Step 2. Reaction conditions: 80°C for 2 days. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 25g $SiO_2$) using $CH_2Cl_2$/MeOH 98/2 to afford 1-(4-chloro-2-fluorobenzyl)-4-methoxy-5-(4-methoxyphenyl)pyridin-2(1*H*)-one (0.10mmol, 36mg, 48%).

LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 4.62min; MS *m/z* (CI) $[MH]^+$= 374, 376; $^1H$ NMR (300 MHz, $CDCl_3$) δ 3.78 (s, 3H), 3.82 (s, 3H), 5.11 (s, 2H), 5.99 (s, 1H), 6.88-6.95 (m, 2H), 7.08-7.15 (m, 2H), 7.20-7.30 (m, 3H), 7.40-7.50 (m, 1H).

**EXAMPLE 34 : 1-(4-(Methoxymethyl)benzyl)-5-(4-methoxyphenyl)pyridin-2(1*H*)-one (Final Compound 4-25)**



*Step 1 : 2-Methoxy-5-(4-methoxyphenyl)pyridine*

According to Scheme 4 Method B: The title compound was prepared according to Example 1 Step 3 from 5-bromo-2-methoxypyridine (12.1mmol, 2.30g) and 4-methoxyphenylboronic acid (18.2mmol, 2.76g), then purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 25g $SiO_2$, $CH_2Cl_2$/MeOH 100/0 to 95/5), yielding the title compound (1.60g, 61%).

LC (XTerra RP18, 3.5µm, 3.0x50mm Column): RT = 3.03min; MS m/z (CI) [MH]+= 216.

*Step 2 : 1-(4-(Hydroxymethyl)benzyl)-5-(4-methoxyphenyl)pyridin-2(1H)-one*

According to Scheme 4 Step 1: The title compound was prepared according to Example 6 Step 2, from 2-methoxy-5-(4-methoxyphenyl)pyridine (1eq, 4.60mmol, 1.00g) and (4-(bromomethyl)phenyl)methanol (1.1eq, 5.10mmol 1.00g). Reaction conditions: 5 hours at 70°C and room temperature overnight. The residue was triturated with pentane, yielding the title compound (3.70mmol, 1.20g, 80%).

LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 3.23min; MS *m/z* (CI) $[MH]^+$= 322.

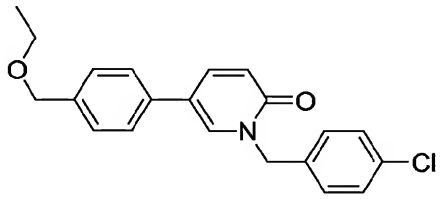
*Step 3 : 1-(4-(Methoxymethyl)benzyl)-5-(4-methoxyphenyl)pyridin-2(1H)-one*

According to Scheme 24 Step 3: A mixture of 1-(4-(hydroxymethyl)benzyl)-5-(4-methoxyphenyl)pyridin-2(1*H*)-one (1eq, 0.25mmol, 0.08g), NaH (55%, 1.5eq, 0.37mmol, 18mg) and iodomethane (3eq, 0.75mmol, 0.11g) in DMF (2mL) was stirred

at room temperature overnight. The crude was diluted with AcOEt. The organic layer was washed with water, dried over $Na_2SO_4$, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 5g $SiO_2$, $CH_2Cl_2$/MeOH 99/1), yielding the title compound (0.14mmol, 46mg, 55%) as white solid.

M.p.: 72°C; LC (Zorbax $C_{18}$, 3.5µm, 4.6x50mm Column): RT = 3.92min; MS *m/z* (CI) $[MH]^+$= 336; $^1H$ NMR (300 MHz, $CDCl_3$) δ 3.25 (s, 3H), 3.77 (s, 3H), 4.36 (s, 2H), 5.15 (s, 2H), 6.50 (d, J=9.3Hz, 1H), 6.98 (d, J=9.0Hz, 2H), 7.25-7.39 (m, 4H), 7.49 (d, J=9.0Hz, 2H), 7.80 (dd, J=2.7Hz and 9.6Hz, 1H), 8.15 (d, J=2.7Hz, 1H).

**EXAMPLE 35 : 1-(4-Chlorobenzyl)-5-(4-(ethoxymethyl)phenyl)pyridin-2(1*H*)-one (Final Compound 2-25)**



*Step 1 : 1-(4-Chlorobenzyl)-5-(4-(hydroxymethyl)phenyl)pyridin-2(1H)-one*

According to Scheme 25 Step 2: The title compound was prepared from 1-(4-chlorobenzyl)-5-bromopyridin-2(1*H*)-one (1eq, 3.30mmol, 1.00g, Example 2 Step 1) and 4-(hydroxymethyl)phenylboronic acid (1.5eq, 5.00mmol, 0.76g) according to the procedure described for Example 1 Step 3. Reaction conditions: overnight at 80°C. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 70g $SiO_2$) using $CH_2Cl_2$/MeOH 98/2 as the eluent to afford 1-(4-chlorobenzyl)-5-(4-(hydroxymethyl)phenyl)pyridin-2(1*H*)-one (1.72mmol, 0.62g, 52%) as a brown oil LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 3.47min; MS *m/z* (CI) $[MH]^+$= 326, 328.

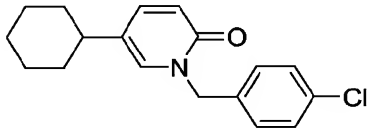
*Step 2 : 1-(4-Chlorobenzyl)-5-(4-(ethoxymethyl)phenyl)pyridin-2(1H)-one*

According to Scheme 25 Method A: The title compound was prepared from 1-(4-chlorobenzyl)-5-(4-(hydroxymethyl)phenyl)pyridin-2(1*H*)-one (1eq, 2.50mmol, 0.80g) and iodoethane (3eq, 7.40mmol, 1.10g) ) according to the procedure described for

Example 34 Step 3. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 5g $SiO_2$) using $CH_2Cl_2$/MeOH 99/1 as eluent to afford 1-(4-chlorobenzyl)-5-(4-(ethoxymethyl)phenyl)pyridin-2(1*H*)-one (1.02mmol, 0.36g, 41%) as a yellow solid.

M.p.: 109°C; LC (Zorbax $C_{18}$, 3.5µm, 4.6x50mm Column): RT = 4.62min; MS *m/z* (CI) $[MH]^+$= 354, 356; $^1H$ NMR (300 MHz, DMSO-$d^6$) δ 1.15 (t, J=6.9Hz, 3H), 3.47 (q, J=6.9Hz, 2H), 4.45 (s, 2H), 5.16 (s, 2H), 6.53 (d, J=9.6Hz, 1H), 7.32-7.40 (4H), 7.55 (d, J=8.4Hz, 2H), 7.85 (dd, J=2.7Hz and 9.3Hz, 1H), 8.28 (d, J=2.7Hz, 1H).

**EXAMPLE 36 : 1-(4-Chlorobenzyl)-5-cyclohexylpyridin-2(1*H*)-one (Final Compound 2-01)**




*Step 1 : 1-(6-Methoxypyridin-3-yl)cyclohexanol*

According to Scheme 26 Step 1: To a stirred solution of 4-bromo-2-methoxypyridine (1eq, 5.30mmol, 1.00g) in anhydrous THF (30mL) at -78°C under nitrogen was added dropwise a solution of butyl lithium (1.3eq, 2.5M solution in hexane, 6.90mmol, 2.8mL). The reaction was then stirred at -78°C for 2 hours. Cyclohexanone (5eq, 27.0mmol, 2.8mL) was then added dropwise over 5 minutes. The reaction was stirred at -78°C for two hours then allowed to warm to room temperature. The reaction was stirred for a further 16 hours then quenched with water. The reaction was evaporated *in vacuo*, redissolved in $CH_2Cl_2$ (100mL) and washed with brine (100mL). The organic phase was extracted, dried over $MgSO_4$, filtered and evaporated to leave a yellow oil. The oil was purified by column chromatography (AIT Flashsmart prepacked column 25g $SiO_2$, pure AcOEt), yielding the title compound (4.10mmol, 0.86g, 78%) as a colorless oil which solidified on standing.

LC (Zorbax $C_{18}$, 3.5µm, 4.6x50mm Column): RT = 3.33min; MS *m/z* (CI) $[MH]^+$= 208.

*Step 2 : 5-Cyclohexenyl-2-methoxypyridine*

According to Scheme 26 Step 2: The title compound was prepared from 1-(6-methoxypyridin-3-yl)cyclohexanol (1eq, 1.21mmol, 0.25g) and methanesulfonyl chloride (4eq, 4.82mmol, 0.37mL) according to the procedure described for Example 4 Step 1. The crude residue was purified by chromatography over silicagel (AIT Flashsmart prepacked column 10g $SiO_2$, AcOEt/pentane 30/10 to pure AcOEt), yielding the title compound (0.76mmol, 0.14g, 63%) as a colorless oil.

LC (Zorbax $C_{18}$, 3.5µm, 4.6x50mm Column): RT = 5.08min; MS *m/z* (CI) $[MH]^+$= 190.

*Step 3 : 5-Cyclohexyl-2-methoxypyridine*

According to Scheme 26 Step 3: The title compound was prepared according to Example 19 Step 2, from 5-cyclohexenyl-2-methoxypyridine (1eq, 0.74mmol, 0.14g). Reaction conditions: 32 hours at room temperature. The residue was purified by chromatography over silicagel (AIT Flashsmart prepacked column 10g $SiO_2$, $CH_2Cl_2$/AcOEt 95/5), yielding the title compound (0.33mmol, 63mg, 45%) as a colorless oil.

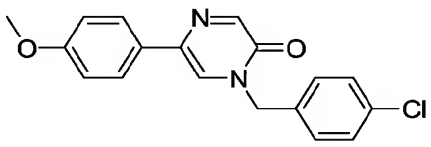
LC (Zorbax $C_{18}$, 3.5µm, 4.6x50mm Column): RT = 5.15min; MS *m/z* (CI) $[MH]^+$= 192.

*Step 4 : 1-(4-Chlorobenzyl)-5-cyclohexylpyridin-2(1H)-one*

According to Scheme 26 Step 4: The title compound was prepared according to Example 6 Step 2, from 5-cyclohexyl-2-methoxypyridine (1eq, 0.30mmol. 57mg) and 1-(bromomethyl)-4-chlorobenzene (1.5eq, 0.44mmol, 92mg), then purified by chromatography over silicagel (AIT Flashsmart prepacked column 5g $SiO_2$, $CH_2Cl_2$/MeOH 98/2) then recrystallized in pentane/diisopropyl ether, yielding the title compound (0.20mmol, 0.09g, 68%) as a beige solid.

M.p.: 72°C; LC (Zorbax $C_{18}$, 3.5µm, 4.6x50mm Column): RT = 5.07min; MS *m/z* (CI) $[MH]^+$= 302, 304; $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.07–1.43 (5H), 1.63-1.86 (5H), 2.13-2.28 (m, 1H), 5.08 (s, 2H), 6.58 (d, J=9.5Hz, 1H), 6.99 (d, J=2.6Hz, 1H), 7.20-7.25 (m, 2H), 7.26-7.30 (m, 2H), 7.31-7.33 (m, 1H).

**EXAMPLE 37 : 1-(4-Chlorobenzyl)-5-(4-methoxyphenyl)pyrazin-2(1*H*)-one (Final Compound 12-06)**



*Step 1 : 1-(4-Chlorobenzyl)-5-bromopyrazin-2(1H)-one*

According to Scheme 27 Step 1: The title compound was prepared from 5-bromopyrazin-2(1*H*)-one (1eq, 2.86mmol, 0.50g) and 1-(bromomethyl)-4-chlorobenzene (1.5eq, 4.29mmol, 0.88g) according to the procedure described for Example 1 Step 2. Reaction conditions: 3 hours at 70°C in acetonitrile. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 25g $SiO_2$) using pure AcOEt as eluent to afford 1-(4-chlorobenzyl)-5-bromopyrazin-2(1*H*)-one (2.48mmol, 0.74g, 87%) as a white solid.

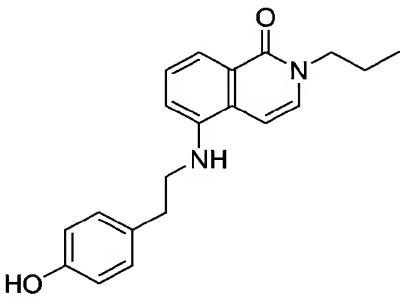
LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 3.91min; MS *m/z* (CI) $[MH]^+$= 300, 302.

*Step 2 : 1-(4-Chlorobenzyl)-5-(4-methoxyphenyl)pyrazin-2(1H)-one*

According to Scheme 27 Step 2: The title compound was prepared from 1-(4-chlorobenzyl)-5-bromopyrazin-2(1*H*)-one (1eq, 0.67mmol, 0.20g) and 4-methoxyphenylboronic acid (1.5eq, 1.00mmol, 0.15g) according to the procedure described for Example 1 Step 3. Reaction conditions: 1 hour at 80°C. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 10g $SiO_2$) using $CH_2Cl_2$/MeOH (98/2) as the eluent to afford 1-(4-chlorobenzyl)-5-(4-methoxyphenyl)pyrazin-2(1*H*)-one (0.47mmol, 0.15g, 71%) as a beige solid.

M.p.: 133°C; LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 4.41min; MS *m/z* (CI) $[MH]^+$= 327, 329. $^1H$ NMR (300 MHz, DMSO-$d^6$) δ 3.78 (s, 3H), 5.12 (s, 2H), 7.00 (d, J=9.0Hz 2H), 7.40-7.50 (m, 4H), 7.77 (d, J=9.0Hz, 2H), 8.14 (s, 1H), 8.39 (s, 1H).

**EXAMPLE 38 : 5-(4-Hydroxyphenethylamino)-2-propylisoquinolin-1(2*H*)-one (Final Compound 13-05)**



*Step 1 : 5-Chloroisoquinoline N-oxide*

According to Scheme 28 Step 1: A solution of MCPBA (1.9, 15.0mmol, 3.6g) and 5-chloroisoquinoline (1eq, 7.80mmol, 1.27g) in $CH_2Cl_2$ (30mL) was stirred for 2 hours at room temperature. The reaction mixture was diluted with $CH_2Cl_2$ (20mL) and MeOH (10mL) and the organic phase was washed with 2M NaOH solution.The aqueous layer was extracted with $CH_2Cl_2$. The organic fractions were combined, dried over $MgSO_4$, filtered and evaporated to yield the title compound (6.20mmol, 1.12g, 79%) as an orange solid.

*Step 2 : 5-Chloroisoquinolin-1(2H)-one*

According to Scheme 28 Step 2: A solution of 5-chloroisoquinoline N-oxide (1eq, 6.88mmol, 1.25g) in anhydride acetic (20mL) was stirred for 3 hours under reflux and overnight at room temperature. After distillation of anhydride acetic, a solution of NaOH (2M, 10mL) was added and the reaction mixture was stirred for 1 hour at 50-60°C. Then the reaction mixture was acidified (pH=6) with citric acid (5% in water). The precipitate was filtered, washed with water, dried under vacuum. The crude residue was taken up in $CH_2Cl_2$ (20mL). The organic phase was washed with brine, dried over $MgSO_4$, filtered and evaporated to yield the title compound (3.73mmol, 0.67g, 100%) as a brown solid.

*Step 3 : 5-Chloro-2-propylisoquinolin-1(2H)-one*

According to Scheme 28 Step 3: The title compound was prepared from 5-chloroisoquinolin-1(2*H*)-one (1eq, 2.66mmol, 0.48g) and 1-bromopropyl (1.1eq,

2.93mmol, 0.27mL) according to the procedure described for Example 1 Step 2. Reaction conditions: microwaved at 150°C for 60 min. in acetone. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 25g $SiO_2$) using pure $CH_2Cl_2$ to afford 5-chloro-2-propylisoquinolin-1(2*H*)-one (1.06mmol, 0.24g, 40%) as an orange solid.

*Step 4 : 5-(4-Methoxyphenethylamino)-2-propylisoquinolin-1(2H)-one*

According to Scheme 28 Step 4: To a mixture of 5-chloro-2-propylisoquinolin-1(2*H*)-one (1eq, 1.08mmol, 0.24g), NaOtBu (1.5eq, 1.62mmol, 0.16g), $Pd_2(dba)_3$ (0.05eq, 54µmol, 50mg), BINAP (0.05eq, 54µmol, 34mg) in degassed and dried toluene (4mL) was added (1.5eq, 1.62mmol, 0.25g). The reaction mixture was microwaved at 180°C for 2 hours and 1 hour at 200°C. The reaction mixture was quenched with water and the aqueous phase was extracted with $CH_2Cl_2$. The organic fraction was washed with saturated $NH_4OH$ solution, brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (AIT Flashsmart prepacked column $SiO_2$, cyclohexane/AcOEt 90/10) to afford 5-(4-methoxyphenethylamino)-2-propylisoquinolin-1(2*H*)-one (0.39mmol, 0.13g, 36%) as a white solid.

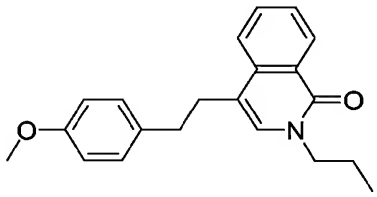
Rf = 0.05 (cyclohexane/AcOEt 80/20); M.p.: 109-110°C; LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 4.60min; MS *m/z* (CI) $[MH]^+$= 337.

*Step 5 : 5-(4-Hydroxyphenethylamino)-2-propylisoquinolin-1(2H)-one*

The title compound was prepared from 5-(4-methoxyphenethylamino)-2-propylisoquinolin-1(2*H*)-one (1eq, 0.20mmol, 66mg) according to the procedure described for Example 20 Step 2. The crude product was purified by trituration in diisopropyl ether to yield after filtration 5-(4-hydroxyphenethylamino)-2-propylisoquinolin-1(2*H*)-one (64µmol, 20mg, 32%) as a brown powder

M.p.: 170-171°C; LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 3.78min; MS *m/z* (CI) $[MH]^+$= 323; $^1H$ NMR (300 MHz, DMSO-$d^6$) δ 0.96 (t, J=7.4Hz, 3H), 1.40-1.72 (br. s, 1H), 1.72-1.87 (m, 2H), 2.99 (t, J=7.2Hz, 2H), 3.47 (t, J=6.9Hz, 2H), 3.95 (t, J=7.4Hz, 2H), 6.35-6.47 (m, 1H), 6.79 (d, J=8.4Hz, 2H), 6.99-7.12 (m, 4H), 7.34-7.42 (m, 1H), 7.91-8.02 (m, 1H).

**EXAMPLE 39 : 4-(4-Methoxyphenethyl)-2-propylisoquinolin-1(2*H*)-one (Final Compound 14-01)**



*Step 1 : 4-(2-(4-Methoxyphenyl)ethynyl)isoquinoline*

According to Scheme 29 Step 1: The title compound was prepared from 4-bromoisoquinoline (1eq, 5.30mmol, 1.10g) and 1-ethynyl-4-methoxybenzene (1eq, 5.30mmol, 0.70g) according to the procedure described for Example 13 Step 1. Reaction conditions: 70°C for 4 hours. The crude product was purified by silica gel chromatography (AIT Flashsmart prepacked column $SiO_2$, cyclohexane/AcOEt 90/10 to 80/20) to afford 4-(2-(4-methoxyphenyl)ethynyl)isoquinoline (3.11mmol, 0.81g, 59%) as a white solid.

LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 5.19min; MS *m/z* (CI) $[MH]^+$= 260.

*Step 2 : 4-(4-Methoxyphenethyl)isoquinoline*

According to Scheme 29 Step 2: The title compound was prepared from 4-(2-(4-methoxyphenyl)ethynyl)isoquinoline (1eq, 3.11mmol, 0.81g) according to the procedure described for Example 13 Step 2. Reaction conditions: overnight at 50°C. The crude product was purified by silica gel chromatography (AIT Flashsmart prepacked column $SiO_2$ 30g, cyclohexane/AcOEt 85/15) to afford 4-(4-methoxyphenethyl)isoquinoline (1.33mmol, 0.35g, 43%) as a yellow oil.

LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 3.26min; MS *m/z* (CI) $[MH]^+$= 264.

*Step 3 : 4-(4-Methoxyphenethyl)isoquinoline-N-oxide*

According to Scheme 29 Step 3: The title compound was prepared from 4-(4-methoxyphenethyl)isoquinoline (1eq, 1.33mmol, 0.35g) according to the procedure described for Example 38 Step 1. The crude product was used without being purified

and yielded 4-(4-methoxyphenethyl)isoquinoline-N-oxide (1.33mmol, 0.37g, 100%) as an orange solid.

*Step 4 : 4-(4-Methoxyphenethyl)isoquinolin-1(2H)-one*

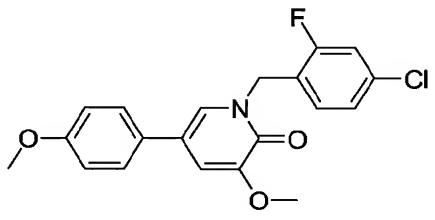
According to Scheme 29 Step 4: The title compound was prepared from 4-(4-methoxyphenethyl)isoquinoline-N-oxide (1eq, 1.33mmol, 0.37g) according to the procedure described for Example 38 Step 2. The crude product was used without being purified and yielded 4-(4-methoxyphenethyl)isoquinolin-1(2*H*)-one (0.36mmol, 0.10g, 27%) as a brown solid.

*Step 5 : 4-(4-Methoxyphenethyl)-2-propylisoquinolin-1(2H)-one*

According to Scheme 29 Step 5: The title compound was prepared from 4-(4-methoxyphenethyl)isoquinolin-1(2*H*)-one (1eq, 0.36mmol, 0.10g) 1-bromopropane (1.5eq, 0.54mmol, 49µL) according to the procedure described for Example 1 Step 2. Reaction conditions: microwaved at 180°C for 15min.The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 25g $SiO_2$) using $CH_2Cl_2$/MeOH 99.5/0.5 to afford 4-(4-methoxyphenethyl)-2-propylisoquinolin-1(2*H*)-one (47µmol, 15mg, 13%) as an orange oil.

LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 4.89min; MS *m/z* (CI) $[MH]^+$= 322; $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.83 (t, J=7.4Hz, 3H), 1.55-1.70 (m, 2H), 2.75-2.90 (4H), 3.72 (s, 3H), 3.81 (t, J=7.3Hz, 2H), 6.60 (s, 1H), 6.75 (d, J=8.7Hz, 2H), 6.97 (d, J=8.6Hz, 2H), 7.40-7.50 (m, 1H), 7.62-7.68 (m, 2H), 8.40-8.45 (m, 1H).

**EXAMPLE 40 : 1-(4-Chloro-2-fluorobenzyl)-3-methoxy-5-(4-methoxyphenyl) pyridin-2(1*H*)-one (Final Compound 9-10)**



*Step 1 : 5-Bromo-2,3-dimethoxypyridine*

The title compound was prepared from 2,3-dimethoxypyridine (1eq, 7.19mmol, 1.00g) according to the procedure described for Example 1 Step 1. Reaction conditions: 48 hours at room temperature. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 25g $SiO_2$) using cyclohexane/AcOEt 96/4 to afford 5-bromo-2,3-dimethoxypyridine (3.81mmol, 0.83g, 53%).

*Step 2 : 2,3-Dimethoxy-5-(4-methoxyphenyl)pyridine*

According to Scheme 4 Method B: The title compound was prepared from 5-bromo-2,3-dimethoxypyridine (1eq, 1.83mmol, 0.40g) and 4-methoxyphenyl boronic acid (1eq, 1.83mmol, 0.28g) according to the procedure described for Example 1 Step 3. The crude product was purified by flash chromatography on silica gel using cyclohexane/AcOEt 90/10 as eluent to afford the title compound 2,3-dimethoxy-5-(4-methoxyphenyl)pyridine (0.82mmol, 0.20g, 45%) was obtained.

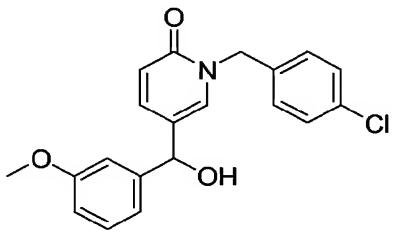
LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 4.27 min; MS *m/z* (CI) $[MH]^+$= 246.

*Step 3 : 1-(4-Chloro-2-fluorobenzyl)-3-methoxy-5-(4-methoxyphenyl)pyridin-2(1H)-one*

According to Scheme 4 Step 1: The title compound was prepared from 2,3-dimethoxy-5-(4-methoxyphenyl)pyridine (1eq, 0.41mol, 0.10g) and 1-(bromomethyl)-4-chloro-2-fluorobenzene (2eq, 0.82mmol, 0.18g) according to the procedure described for Example 6 Step 2. Reaction conditions: 14 hours at 80°C in acetonitrile. The crude product was purified by silica gel chromatography (AIT Flashsmart prepacked column 10g $SiO_2$) using cyclohexane/AcOEt 70/30 to 50/50 as eluent to afford 1-(4-Chloro-2-fluorobenzyl)-3-methoxy-5-(4-methoxyphenyl)pyridin-2(1*H*)-one (0.24mmol, 0.09g, 59%).

LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 4.53min; MS *m/z* (CI) $[MH]^+$= 374, 376; $^1H$ NMR (300MHz, $CDCl_3$) δ 3.83 (s, 3H), 3.87 (s, 3H), 5.22 (s, 2H), 6.82 (d, J=2.3Hz, 1H), 6.95 (d, J=8.7Hz, 2H), 7.07-7.12 (m, 2H), 7.13-7.15 (m, 1H), 7.32 (d, J=9.0Hz, 2H), 7.47-7.55 (m, 1H).

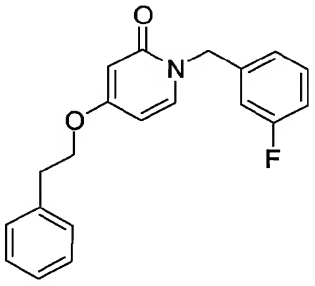
**EXAMPLE 41 : 1-(4-Chlorobenzyl)-5-(hydroxy(3-methoxyphenyl)methyl)pyridin-2(1*H*)-one (Final Compound 3-10)**



According to Scheme 7 Method B: A solution of 3-methoxybenzylmagnesium bromide (1.2eq, 1.00mmol, 1.00mL) was added dropwise to a solution of 1-(4-chlorobenzyl)-1,6-dihydro-6-oxopyridine-3-carbaldehyde (1eq, 1.21mmol, 0.30g, Example 10 Step 1) in THF (15mL) at -78°C under a nitrogen atmosphere. The reaction mixture was stirred for 14 hours at room temperature. The resulting mixture was poured onto ice and extracted with $CH_2Cl_2$. The organic layer was dried over $MgSO_4$, filtered and evaporated. Purification by flash chromatography (AIT Flashsmart prepacked column 25g $SiO_2$, $CH_2Cl_2$/AcOEt 80/20 to 70/30) afford 1-(4-chlorobenzyl)-5-(hydroxy(3-methoxyphenyl)methyl)pyridin-2(1*H*)-one (0.64mmol, 0.28g, 64%) as a yellow semi-solid.

LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 3.76 min; MS *m/z* $ES^+$= 356, 358; $^1H$ NMR (500MHz, $CDCl_3$) δ 2.13 (d, J=3.4Hz, 1H), 3.80 (s, 3H), 5.09 (s, 2H), 5.56 (d, J=3.5Hz, 1H), 6.57 (d, J=9.4Hz, 1H), 6.84-6.90 (3H), 7.22-7.35 (5H).

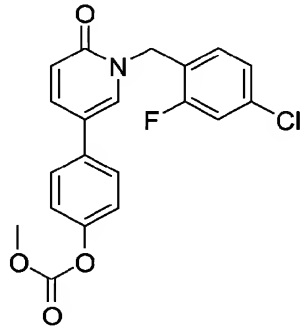
**EXAMPLE 42 : 1-(3-Fluorobenzyl)-4-phenethoxypyridin-2(1*H*)-one (Final Compound 7-03)**



According to Scheme 13 Method A: The title compound was prepared from 1-(3-fluorobenzyl)-4-hydroxypyridin-2(1*H*)-one (1eq, 0.23mmol, 0.05g, Example 19 Step 2) and 1-(2-bromoethyl)benzene (2eq, 0.46mmol, 0.06mL) according to the procedure described for Example 1 Step 2. Microwave conditions: 180°C for 900s in acetonitrile (2mL). The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 25g $SiO_2$) using $CH_2Cl_2$/AcOEt 80/20 and by recristallization in pentane to afford 1-(3-fluorobenzyl)-4-phenethoxypyridin-2(1*H*)-one (0.13mmol, 43mg, 58%) as a white solid.

M.p.: 93°C; LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 4.41min; MS *m/z* (CI) $[MH]^+$= 324; $^1H$ NMR (500MHz, DMSO-$d^6$) δ 3.00 (t, J=6.7Hz, 2H), 4.18 (t, J=6.7Hz, 2H), 5.01 (s, 2H), 5.84 (d, J=2.7Hz, 1H), 5.95 (dd, J=2.7Hz and 7.6Hz, 1H), 7.03-7.11 (3H), 7.18-7.25 (m, 1H), 7.29 (d, J=4.7Hz, 4H), 7.32-7.38 (m, 1H), 7.66 (d, J=7.6Hz, 1H).

**EXAMPLE 43 : 4-(1-(4-Chloro-2-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl) phenyl methyl carbonate (Final Compound 6-39)**

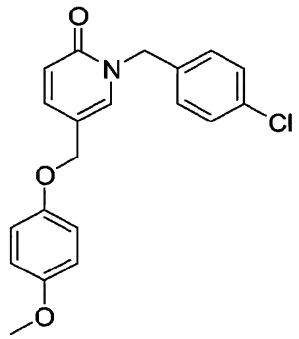



According to Scheme 14 Method B: A suspension of 1-(4-chloro-2-fluorobenzyl)-5-(4-hydroxyphenyl)pyridin-2(1*H*)-one (1eq, 0.61mmol, 0.20g, Example 20 Step 2), $K_2CO_3$ (10eq, 6.10mmol, 0.84g) and methylchloroformate (4eq, 2.43mmol, 0.19mL) in THF (10mL) was stirred overnight at room temperature. Water was added to the reaction mixture, then the aqueous phase was extracted with AcOEt. The organic phase was dried over $MgSO_4$, filtered and evaporated. The resulting crude oil was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 10g $SiO_2$) using $CH_2Cl_2$/AcOEt 90/10 then was washed with $Et_2O$ and was dried to afford 4-(1-(4-

chloro-2-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)phenyl methyl carbonate (0.36mmol, 139mg, 59%) as a white solid.

M.p.: 124°C; LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 4.28min; MS *m/z* (CI) $[MH]^+$= 388, 390; $^1H$ NMR (300MHz, $CDCl_3$) δ 3.84 (s, 3H), 5.19 (s, 2H), 6.53 (d, J=9.6Hz, 1H), 7.17-7.27 (m, 2H), 7.27-7.33 (3H), 7.45 (dd, J=2.1Hz and 9.9Hz, 1H), 7.58-7.66 (m, 2H), 7.88 (dd, J=2.7Hz and 9.9Hz, 1H), 8.23 (d, J=2.7Hz, 1H).

**EXAMPLE 44 : 1-(4-Chlorobenzyl)-5-((4-methoxyphenoxy)methyl)pyridin-2(1*H*)-one (Final Compound 16-02)**



*Step 1 : 1-(4-Chlorobenzyl)-5-(hydroxymethyl)pyridin-2(1H)-one*

According to Scheme 16 Method B: A solution of 1-(4-chlorobenzyl)-6-oxo-1,6-dihydropyridine-3-carbaldehyde (1eq, 1.41mmol, 0.35g, Example 10 Step 1) and DIBAL (3eq, 4.20mmol, 4.20mL) in THF (5mL) was stirred for 30 min. at -78°C and 1 hour at room temperature. After addition of AcOEt, the reaction mixture was diluted with water. The organic layer was washed with saturated $NH_4Cl$ solution, dried over $Na_2SO_4$, filtered through celite and evaporated. The resulting crude residue was purified by silica gel chromatography (AIT Flashsmart prepacked column 25g $SiO_2$) using $CH_2Cl_2$/MeOH 95/5 to afford 1-(4-chlorobenzyl)-5-(hydroxymethyl)pyridin-2(1*H*)-one (0.45mmol, 0.11g, 32%) as an orange oil.

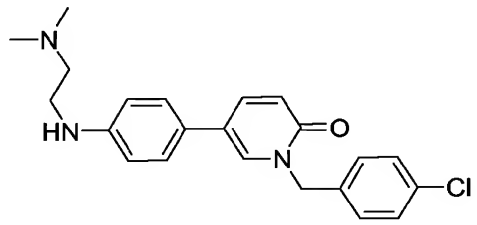
LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 2.86min; MS *m/z* (CI) $[MH]^+$= 250, 252.

*Step 2 : 1-(4-Chlorobenzyl)-5-((4-methoxyphenoxy)methyl)pyridin-2(1H)-one*

According to Scheme 16 Method B: 4-Methoxyphenol (1.5eq, 0.68mmol, 84.3mg), $PPh_3$ (2.0eq, 0.91mmol, 0.30g) and DEAD (2eq, 0.91mmol, 0.16g) were added to a solution of 1-(4-chlorobenzyl)-5-(hydroxymethyl)pyridin-2(1*H*)-one (1eq, 0.45mmol, 0.11g) in THF (5mL). The reaction mixture was stirred overnight at room temperature. After evaporation of the solvent, the reaction mixture was diluted with water. The organic layer was washed with saturated $NaHCO_3$ solution, dried over $Na_2SO_4$, filtered and evaporated. The crude product was purified by silica gel chromatography (AIT Flashsmart prepacked column 25g $SiO_2$) using cyclohexane/AcOEt 80/20 to afford 1-(4-chlorobenzyl)-5-((4-methoxyphenoxy)methyl)pyridin-2(1*H*)-one (0.19mmol, 0.07g, 42%) as a white solid.

M.p.: 114°C. LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 4.36min; MS *m/z* (CI) $[MH]^+$= 356, 358. $^1H$ NMR (500MHz, DMSO-$d^6$) δ 3.69 (s, 3H), 4.74 (s, 2H), 5.07 (s, 2H), 6.45 (d, J=9.3Hz, 1H), 6.82-6.87 (m, 2H), 6.88-6.93 (m, 2H), 7.29 (d, J=8.5Hz, 2H), 7.40 (d, J=8.5Hz, 2H), 7.52 (dd, J=2.5Hz and 9.0Hz, 1H), 7.93 (d, J=2.3Hz, 1H).

**EXAMPLE 45 : 1-(4-Chlorobenzyl)-5-(4-(2-(dimethylamino)ethylamino)phenyl) pyridin-2(1*H*)-one (Final Compound 2-50)**



*Step 1 : tert-Butyl 4-(1-(4-chlorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)phenyl carbamate*

According to Scheme 19 Step 1: A suspension of 1-(4-chlorobenzyl)-5-bromopyridin-2(1*H*)-one (3.35mmol, 1.00g, Example 2 Step 1), N-*tert*-butoxycarbonyl-4-aminophenylboronic acid (6.03mmol, 1.42g), $Pd(PPh_3)_4$ (0.17mmol, 195mg), $Na_2CO_3$ (13.4mmol, 1.42g) in DME (20mL) and $H_2O$ (5mL) was degassed to remove the oxygen. The mixture was heated at 85°C for 20 hours. The resulting suspension was filtered off and the filtrate was washed with $CH_2Cl_2$. The organic solvent was

separated, dried ($Na_2SO_4$) and the solvent was evaporated under reduced pressure. The residue was purified in a manifold (vac.) using a Sep-Pak silica cartridge $CH_2Cl_2$/MeOH($NH_3$)sat. 98/2. The product fractions were collected and the solvent was evaporated to yield the title compound (627mg, 46%).

*Step 2 : tert-Butyl 4-(1-(4-chlorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)phenyl(2-(dimethylamino)ethyl)carbamate*

According to Scheme 19 Step 4: *tert*-Butyl 4-(1-(4-chlorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)phenylcarbamate (0.34mmol 0.14g) was dissolved in dry THF (4mL) and the resulting solution was cooled at 0°C. Then, NaH (60% mineral oil; 1.02mmol, 40.8mg) was added, the mixture was stirred at 0°C for 10 minutes, warmed at room temperature and stirred for 30 minutes. After, N,N-dimethylaminoethyl chloride (0.69mmol) and KI (0.34mmol, 57.0mg) were added and the reaction mixture was heated at 90°C for 16 hours. The resulting suspension was taken up in $CH_2Cl_2$, washed with water, washed with brine, filtered off and the filtrate was washed with $CH_2Cl_2$. The organic solvent was separated, dried ($Na_2SO_4$) and the solvent was evaporated under reduced pressure. The residue was purified in a manifold (vac.) using a Sep-Pak silica cartridge ($CH_2Cl_2$/MeOH($NH_3$)sat. 95/5). The product fractions were collected and the solvent was evaporated to yield *tert*-butyl 4-(1-(4-chlorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)phenyl(2-(dimethylamino)ethyl)carbamate (87.9mg)

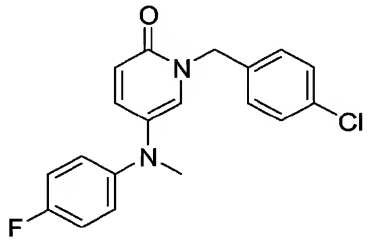
*Step 3 : 1-(4-Chlorobenzyl)-5-(4-(2-(dimethylamino)ethylamino)phenyl)pyridin-2(1H)-one*

According to Scheme 19 Step 5: *tert*-Butyl 4-(1-(4-chlorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)phenyl(2-(dimethylamino)ethyl)carbamate (0.16mmol, 79.0mg) was dissolved in dry $CH_2Cl_2$ (30mL). Then TFA (7mL) was added dropwise and the resulting solution was stirred at room temperature for 3 hours. Then the solvent was evaporated under reduced pressure and the resulting residue thus obtained was resulting suspension was taken up in $CH_2Cl_2$, washed with a saturated aqueous $NaHCO_3$ solution. The organic solvent was separated, dried ($Na_2SO_4$) and the solvent was evaporated under reduced pressure. The residue was purified in a manifold (vac.) using a Sep-Pak silica cartridge $CH_2Cl_2$/MeOH($NH_3$)sat. 95/5. The product fractions were

collected and the solvent was evaporated to yield 1-(4-chlorobenzyl)-5-(4-(2-(dimethylamino)ethylamino)phenyl)pyridin-2(1*H*)-one (16.4mg, 26%)

LC (ACE Column): RT = 3.23min; MS *m/z* (CI) $[MH]^+$= 382; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, 1H, *J*=9.5, 2.6 Hz); 7.34 (d, 1H, *J*=2.6 Hz); 7.26-7.33 (m, 4H); 7.17 (d, 2H, *J*=8.7 Hz); 6.67 (d, 1H, *J*=9.5 Hz); 6.64 (d, 2H, *J*=8.4 Hz); 5.15 (s, 2H); 4.43 (s, 1H); 3.16 (t, 2H, *J*=5.8 Hz); 2.58 (t, 2H, *J*=5.8 Hz); 2.27 (s, 6H).

**EXAMPLE 46 : 1-(4-Chlorobenzyl)-5-((4-fluorophenyl)(methyl)amino)pyridin-2(1*H*)-one (Final Compound 3-21)**




*Step 1 : N-(4-Fluorophenyl)-6-methoxy-N-methylpyridin-3-amine*

According to Scheme 22 Method B: To a mixture of 5-bromo-2-methoxypyridine (1eq, 1.06mmol, 0.14mL), KOtBu (1.5eq, 1.60mmol, 0.18g), $Pd(OAc)_2$ (0.02eq, 21μmol, 48mg), BINAP (0.04eq, 42μmol, 26mg) in degassed DMF (1.5mL) was added 4-fluoro-N-methylbenzenamine (1.2eq, 1.28mmol, 0.14mL). The reaction mixture was microwaved at 130°C for 5min. The reaction mixture was quenched with water and the aqueous phase was extracted with AcOEt. The organic fraction was washed brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (AIT Flashsmart prepacked column 15g $SiO_2$, $CH_2Cl_2$/AcOEt 90/10) to afford N-(4-fluorophenyl)-6-methoxy-N-methylpyridin-3-amine (0.08mmol, 20mg, 8%) as a yellow oil.

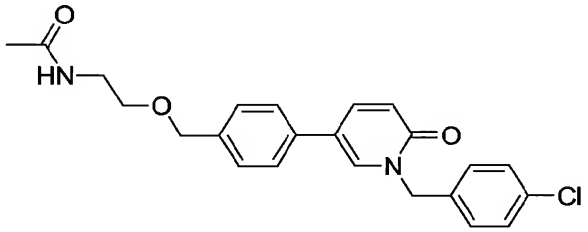
Rf = 0.45 ($CH_2Cl_2$/AcOEt 80/20); LC (XTerra $RP_{18}$, 3.5μm, 3.0x50mm Column): RT = 2.49min; MS *m/z* (CI) $[MH]^+$= 233.

*Step 2 : 1-(4-Chlorobenzyl)-5-((4-fluorophenyl)(methyl)amino)pyridin-2(1H)-one*

According to Scheme 22 Step 2: The title compound was prepared from N-(4-fluorophenyl)-6-methoxy-N-methylpyridin-3-amine (1eq, 86μmol, 20mg) and 4-

chloro-benzylbromide (1.7eq, 0.15mmol, 30mg) according to the procedure described for Example 6 Step 2. Reaction conditions: 12 hours at 80°C in acetonitrile. The crude product was purified by silica gel chromatography (AIT Flashsmart prepacked column 10g $SiO_2$) using $CH_2Cl_2$/AcOEt 50/50 as eluent to afford 1-(4-chlorobenzyl)-5-((4-fluorophenyl)(methyl)amino)pyridin-2(1*H*)-one (29µmol, 10mg, 34%) as a yellow oil.
Rf = 0.20 ($CH_2Cl_2$/AcOEt 90/10); LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 4.36min; MS *m/z* (CI) $[MH]^+$= 343, 345; $^1H$ NMR (300MHz, $CDCl_3$) δ 3.24 (s, 3H), 5.02 (s, 2H), 5.56 (dd, J=2.7Hz and 7.7Hz, 1H), 5.74 (d, J=2.7Hz, 1H), 6.92 (d, J=7.7Hz, 1H), 7.07-7.12 (m, 2H), 7.13-7.18 (m, 2H), 7.23 (d, J=8.4Hz, 2H), 7.30 (d, J=8.4Hz, 2H).

**EXAMPLE 47 : *N*-(2-(4-(1-(4-Chlorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl) benzyloxy)ethyl)acetamide (Final Compound 2-42)**



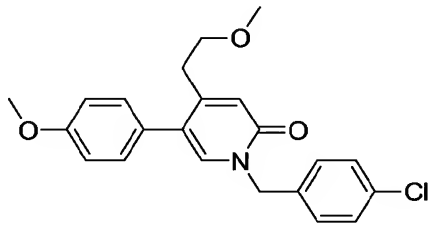
*Step 1 : 1-(4-Chlorobenzyl)-5-(4-(bromomethyl)phenyl)pyridin-2(1H)-one*
According to Scheme 25 Step 3: To a solution of 1-(4-chlorobenzyl)-5-(4-(hydroxymethyl)phenyl)pyridin-2(1*H*)-one (1eq, 3.07mmol, 1.00g, Example 35 Step 1) in THF (8mL) were added NBS (1.22eq, 3.74mmol, 0.67g) and $PPh_3$ (1.20eq, 3.68mmol, 0.97g) at -20°C for 4 hours. After evaporation of the solvent, the crude product was purified by silica gel chromatography (AIT Flashsmart prepacked column 50g $SiO_2$) using $CH_2Cl_2$/MeOH 98/2 to afford 1-(4-chlorobenzyl)-5-(4-(bromomethyl)phenyl)pyridin-2(1*H*)-one (2.06mmol, 0.80g, 67%).
LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 4.71min; MS *m/z* (CI) $[MH]^+$= 388, 390.

*Step 2 : N-(2-(4-(1-(4-Chlorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)benzyloxy)ethyl) acetamide*

According to Scheme 25 Step 4: The title compound was prepared from 1-(4-chlorobenzyl)-5-(4-(bromomethyl)phenyl)pyridin-2(1*H*)-one (1eq, 0.26mmol, 0.10g) and (1.5eq, 0.39mmol, 0.04g) according to the procedure described for Example 34 Step 3. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 5g $SiO_2$) using $CH_2Cl_2$/MeOH 98/2 as the eluent to afford *N*-(2-(4-(1-(4-chlorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)benzyloxy)ethyl) acetamide (0.13mmol, 54mg, 51%) as a white solid.

M.p.:152°C; LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 3.55min; MS *m/z* (CI) $[MH]^+$= 411, 413; $^1H$ NMR (300MHz, DMSO-$d^6$) δ 1.80 (s, 3H), 3.18-3.27 (m, 2H), 3.42 (t, J=6.0Hz, 2H), 4.48 (s, 2H), 5.16 (s, 2H), 6.52 (d, J=9.6Hz, 1H), 7.35-7.42 (6H), 7.56 (d, J=7.8Hz, 2H), 7.86 (dd, J=2.7Hz and 9.6Hz, 2H), 8.28 (d, J= 2.7Hz, 1H).

**Example 48 : 1-(4-Chlorobenzyl)-4-(2-methoxyethyl)-5-(4-methoxyphenyl)pyridin-2(1*H*)-one (Final Compound 9-17)**



*Step 1 : 2-Methoxy-5-(4-methoxyphenyl)-4-methylpyridine*

According to Scheme 30 Step 1: The title compound was prepared from 5-bromo-2-methoxy-4-methylpyridine (1eq, 15.8mmol, 3.20g) and 4-methoxyphenylboronic acid (1.5eq, 23.8mmol, 3.61g) according to the procedure described for Example 1 Step 3. Reaction conditions: 21 hours at 80°C. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 130g $SiO_2$) using AcOEt/MeOH (95/5) as the eluent to afford 2-methoxy-5-(4-methoxyphenyl)-4-methylpyridine (12.8mmol, 2.94g, 81%) as a light yellow solid.

LC (Zorbax $C_{18}$, 3.5µm, 4.60x50mm Column): RT = 4.52min; MS *m/z* (CI) $[MH]^+$= 230.

*Step 2 : 2-(2-Methoxy-5-(4-methoxyphenyl)pyridin-4-yl)ethanol*

According to Scheme 30 Step 2: To a stirred solution of 2-methoxy-5-(4-methoxyphenyl)-4-methylpyridine (1eq, 10.0mmol, 2.30g) in anhydrous THF (66mL) at -78°C under argon was added dropwise butyl lithium (2.5M, 1.5eq, 15.1mmol, 6.0mL). The reaction mixture was stirred for one hour and then allowed to warm slowly to 0°C and stirred at 0°C for a further 30 minutes. The reaction mixture was then cooled to -78°C and paraformaldehyde (6.07g) was added. The reaction mixture was then allowed to warm to room temperature and was stirred for 2 hours. The reaction was quenched with saturated aqueous $NH_4Cl$ (30mL), diluted with AcOEt and the aqueous phase was extracted (x3). The combined organic fractions were dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. HCl 3M (15mL) was added to the solution of the crude residue diluted in acetonitrile (10mL).The reaction mixture was stirred for 2 hours at 60°C. The aqueous phase was extracted with $Et_2O$, then neutralized with $NaHCO_3$ (40mL). The aqueous phase was extracted with $CH_2Cl_2$. The combined organic fractions were dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 20g $SiO_2$) using $CH_2Cl_2$/AcOEt (99/1) as the eluent to afford 2-(2-methoxy-5-(4-methoxyphenyl)pyridin-4-yl)ethanol (0.62mmol, 0.16g, 6%) as a colorless oil.

LC (Zorbax $C_{18}$, 3.5µm, 4.6x50mm Column): RT = 3.42min; MS *m/z* (CI) $[MH]^+$= 260.

*Step 3 : 1-(4-Chlorobenzyl)-4-(2-hydroxyethyl)-5-(4-methoxyphenyl)pyridin-2(1H)-one*

According to Scheme 30 Step 3: The title compound was prepared from 2-(2-methoxy-5-(4-methoxyphenyl)pyridin-4-yl)ethanol (1eq, 0.62mmol, 0.16g) and 1-(bromomethyl)-4-chlorobenzene (1.5eq, 0.93mmol, 0.19g) according to the procedure described for Example 6 Step 2. Reaction conditions: 19 hours under 90°C. The crude product was purified by silica gel chromatography (AIT Flashsmart prepacked column 10g $SiO_2$) using $CH_2Cl_2$/MeOH 98/2 as eluent afford 1-(4-chlorobenzyl)-4-(2-hydroxyethyl)-5-(4-methoxyphenyl)pyridin-2(1*H*)-one (0.22mmol, 82mg, 36%) as a pale yellow solid.

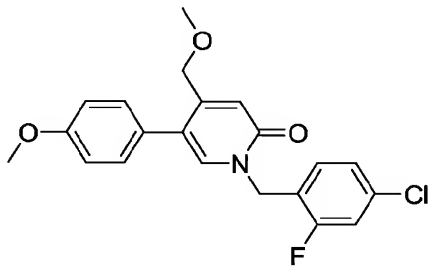
LC (Zorbax $C_{18}$, 3.5µm, 4.6x50mm Column): RT = 3.83min; MS *m/z* (CI) $[MH]^+$= 370, 372.

*Step 4 : 1-(4-Chlorobenzyl)-4-(2-methoxyethyl)-5-(4-methoxyphenyl)pyridin-2(1H)-one*

According to Scheme 30 Step 4: The title compound was prepared from 1-(4-chlorobenzyl)-4-(2-hydroxyethyl)-5-(4-methoxyphenyl)pyridin-2(1*H*)-one (1eq, 0.14mmol, 50mg) and iodomethane (3eq, 0.41mmol, 58mg) according to the procedure described for Example 34 Step 3. The product was further purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 5g $SiO_2$) using $Et_2O$/pentane 90/10 to afford 1-(4-chlorobenzyl)-4-(2-methoxyethyl)-5-(4-methoxyphenyl)pyridin-2(1*H*)-one (0.12mmol, 47mg, 91%) as a colorless oil.

LC (Zorbax $C_{18}$, 3.5µm, 4.6x50mm Column): RT = 4.49min; MS *m/z* (CI) $[MH]^+$= 384, 386; $^1H$ NMR (300MHz, $CDCl_3$) δ 2.65 (t, J=6.7Hz, 2H), 3.25 (s, 3H), 3.44 (t, J=6.7Hz, 2H), 3.82 (s, 3H), 5.09 (s, 2H), 6.58 (s, 1H), 6.90 (d, J=8.7Hz, 2H), 7.06 (s, 1H), 7.11 (d, J=8.7Hz, 2H), 7.23-7.32 (4H).

**EXAMPLE 49 : 1-(4-Chloro-2-fluorobenzyl)-4-(methoxymethyl)-5-(4-methoxyphenyl)pyridin-2(1*H*)-one (Final Compound 9-16)**




*Step 1 : 4-(Bromomethyl)-2-methoxy-5-(4-methoxyphenyl)pyridine*

According to Scheme 31 Step 2: To a solution of 2-methoxy-5-(4-methoxyphenyl)-4-methylpyridine (2.20mmol, 0.50g, Example 48 Step 1) in $CCl_4$ (10mL) was added NBS (2eq, 4.40mmol, 0.78g). The reaction was then heated to reflux and subjected to UV light for 48 hours. The reaction was allowed to cool, filtered and concentrated under reduced pressure to afford crude 4-(bromomethyl)-2-methoxy-5-(4-methoxyphenyl)pyridine (0.70g) as a yellow oil which was used without any purification in the next step.

LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 4.87min; MS *m/z* (CI) $[MH]^+$= 307, 309.

*Step 2 : 2-Methoxy-4-(methoxymethyl)-5-(4-methoxyphenyl)pyridine*

According to Scheme 31 Step 3: The title compound was prepared from 4-(bromomethyl)-2-methoxy-5-(4-methoxyphenyl)pyridine (1eq, 2.30mmol, 0.70g) according to the procedure described for Example 33 Step 1. After work up, 2-methoxy-4-(methoxymethyl)-5-(4-methoxyphenyl)pyridine (0.66mmol, 0.17g) as a light yellow oil.

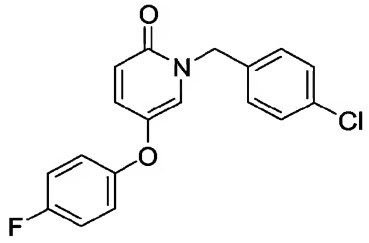
LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 4.56min; MS *m/z* (CI) $[MH]^+$= 260.

*Step 3 : 1-(4-Chloro-2-fluorobenzyl)-4-(methoxymethyl)-5-(4-methoxyphenyl)pyridin-2(1H)-one*

According to Scheme 31 Step 4: The title compound was prepared from 2-methoxy-4-(methoxymethyl)-5-(4-methoxyphenyl)pyridine (1eq, 0.66mmol, 0.17g) and 1-(bromomethyl)-4-chloro-2-fluorobenzene (1.5eq, 0.98mmol, 0.22g) according to the procedure described for Example 6 Step 2. Reaction conditions: 12 hours at 80°C. The crude product was purified by silica gel chromatography (AIT Flashsmart prepacked column 25g $SiO_2$) using $CH_2Cl_2$/MeOH 98/2 as the eluent to afford 1-(4-chloro-2-fluorobenzyl)-4-(methoxymethyl)-5-(4-methoxyphenyl)pyridin-2(1*H*)-one (5µmol, 2mg, 1%) as yellow oil.

LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 3.83min; MS *m/z* (CI) $[MH]^+$= 388, 390; $^1H$ NMR (300MHz, $CDCl_3$) δ 1.64 (s, 2H), 2.07 (s, 3H), 3.83 (s, 3H), 5.12 (s, 2H), 6.48 (s, 1H), 6.93 (d, J=9.0Hz, 2H), 7.13-7.28 (m, 5H), 7.40-7.46 (m, 1H).

**EXAMPLE 50 : 1-(4-Chlorobenzyl)-5-(4-fluorophenoxy)pyridin-2(1*H*)-one (Final Compound 3-13)**



*Step 1 : 5-(4-Fluorophenoxy)-2-methoxypyridine*

According to Scheme 32 Method A: 5-Bromo-2-methoxypyridine (5.32mmol, 1.00g), 4-fluorobenzylalcohol (7.98mmol, 0.90g), N,N-dimethylaminoacetic acid (15.9mmol, 1.69g), CuI (5.32mmol, 1.01g), $CsCO_3$ (12.4mmol, 4.05g) in dioxane (25mL) and DMF (2.5mL) were heated at 150°C for 25 min. under microwave irradiation conditions. Then the cooled crude reaction was filtered off over celite. The filtrate was washed with saturated aqueous $NH_4Cl$ solution and extracted with AcOEt. The organic layer was separated, dried ($Na_2SO_4$) and the solvent was evaporated under reduced pressure. The residue was purified in a manifold (vac.) using a Sep-Pak silica cartridge (heptane/AcOEt, 80/20). The product fractions were collected and the solvent was evaporated to give a mixture of the desired product contaminated with 4-fluorobenzylalcohol. This residue was taken up in AcOEt and washed with aqueous solution of NaOH 1N. The organic layer was separated, dried ($Na_2SO_4$) and the solvent was evaporated under reduced pressure giving 5-(4-fluorophenoxy)-2-methoxypyridine (520mg, 45%).

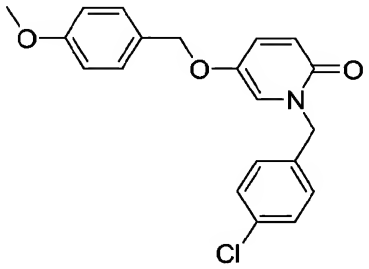
*Step 2 : 1-(4-Chlorobenzyl)-5-(4-fluorophenoxy)pyridin-2(1H)-one*

According to Scheme 32 Step 1: 5-(4-Fluorophenoxy)-2-methoxypyridine (2.37mmol, 520mg), 4-chlorobenzylchloride (3.55mmol, 603mg), NaI (2.37mmol, 356mg) in acetonitrile (15mL) was heated at 150°C for 20 minutes under microwave conditions. The cooled crude reaction was washed with water, extracted with AcOEt. The organic layer was collected, dried ($Na_2SO_4$) and the solvent was evaporated under reduced pressure. The residue was purified in a manifold (vac.) using a Sep-Pak silica cartridge (heptane/AcOEt, 90:10 to $CH_2Cl_2$) and then $CH_2Cl_2$/acetone 90:10), following HPLC

purification yielding 1-(4-chlorobenzyl)-5-(4-fluorophenoxy)pyridin-2(1*H*)-one (211mg, 27%).

LC (ACE Column): RT = 4.56min; MS *m/z* (CI) $[MH]^+$= 330.

**EXAMPLE 51 : 1-(4-Chlorobenzyl)-5-(4-methoxybenzyloxy)pyridin-2(1*H*)-one (Final Compound 3-17)**



*Step 1 : 2-Methoxy-5-(4-methoxybenzyloxy)pyridine*

According to Scheme 32 Method B: To a mixture of 2-methoxy-5-hydroxypyridine (2.87mmol, 0.36g), 4-methoxybenzyl alcohol (5.75mmol, 0.72mL) and $PPh_3$ (5.29mmol, 1.4g) in THF (3.75mL) cooled with an ice-water bath, was added dropwise DEAD (5.47mmol, 0.86ml). The resulting mixture was irradiated under microwave conditions at 90°C for 30 minutes. The resulting reaction mixture was cooled, washed with a 1 N NaOH solution and extracted with AcOEt. The organic layer was separated, dried ($Na_2SO_4$) and the solvent was evaporated under reduced pressure. The residue triturated with diisopropyl ether. The precipitated obtained ($PPh_3O$) was filtered off. The residue was purified in a manifold (vac.) using a Sep-Pak silica cartridge heptane/$CH_2Cl_2$ 80/20 yielding 2-methoxy-5-(4-methoxybenzyloxy)pyridine (339mg, 48%).

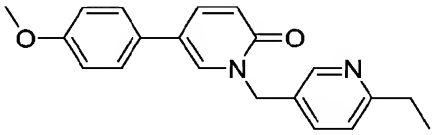
*Step 2 : 1-(4-Chlorobenzyl)-5-(4-methoxybenzyloxy)pyridine-2(1H)-one*

According to Scheme 32 Step 1: 2-Methoxy-5-(4-methoxybenzyloxy)pyridine (1.38mmol, 339mg), 4-chlorobenzylchloride (2.76mmol, 468mg), NaI (1.38mmol, 207mg) in acetonitrile (15mL) was heated at 150°C for 50 minutes under microwave conditions. The cooled crude reaction was washed with water, extracted with AcOEt. The organic layer was collected, dried ($Na_2SO_4$) and the solvent was evaporated under reduced pressure. The residue was purified in a manifold (vac.) using a Sep-Pak silica

cartridge $CH_2Cl_2$ and $CH_2Cl_2$/acetone 90/10) yielding 1-(4-chlorobenzyl)-5-(4-methoxybenzyloxy)pyridine-2(1*H*)-one (141mg, 29%).

LC (ACE Column): RT = 4.39min; MS *m/z* (CI) $[MH]^+$= 355; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.27-7.32 (m, 2H); 7.19-7.25 (m, 3H); 7.14-7.19 (m, 2H, *J*=8.3 Hz); 6.85-6.90 (m, 2H); 6.72 (d, 1H, *J*=3.1 Hz); 6.58 (d, 1H, *J*=9.7 Hz); 5.03 (s, 2H); 4.75 (s, 2H); 3.82 (s, 3H)

**EXAMPLE 52 : 1-((6-Ethylpyridin-3-yl)methyl)-5-(4-methoxyphenyl)pyridin-2(1*H*)-one (Final Compound 4-45)**



*Step 1 : 1-((6-Chloropyridin-3-yl)methyl)-5-(4-methoxyphenyl)pyridin-2(1H)-one*

5-(4-Methoxyphenyl)pyridine-2(1*H*)-one (4.20mmol, 0.85g), 2-chloro-5-(chloromethyl)pyridine (1.5eq, 6.30mmol, 1.02g), $K_2CO_3$ (2eq, 8.40mmol, 1.17g) in THF (10mL) were heated at 70°C for 2 hours. Then, the reaction was cooled to room temperature. The suspension was filtered off and the filtrate was evaporated under reduced pressure. The residue was puridied by short open column chromatography $CH_2Cl_2$/MeOH($NH_3$)sat. 1% yielding 1-((6-chloropyridin-3-yl)methyl)-5-(4-methoxyphenyl)pyridin-2(1*H*)-one as white solid (1.04g, 75%)

*Step 2 : 1-((6-Iodopyridin-3-yl)methyl)-5-(4-methoxyphenyl)pyridin-2(1H)-one*

According to Scheme 33 Step 1: 1-((6-Chloropyridin-3-yl)methyl)-5-(4-methoxyphenyl)pyridin-2(1*H*)-one (2.54mmol, 0.83g), trimethylsilyl chloride (3.3mmol, 0.42mL) and NaI (7.60mmol, 1.14g) in propionitrile (20mL) were heated at 140°C for 20 minutes under microwave irradiation conditions. Then the suspension was filtered off and the solid obtained was partitioned between $CH_2Cl_2$/water. The aqueous layer was extracted several times with $CH_2Cl_2$; the organic layers were combined, dried ($Na_2SO_4$) and the solvent was evaporated under reduced pressure. The residue was treated with $Et_2O$ giving an 1-((6-iodopyridin-3-yl)methyl)-5-(4-methoxyphenyl)pyridin-2(1*H*)-one (600mg, 61%) as a pale grey solid.

*Step 3 : 5-(4-Methoxyphenyl)-1-((6-(2-(trimethylsilyl)ethynyl)pyridin-3-yl)methyl) pyridin-2(1H)-one*

According to Scheme 33 Step 2: A mixture of 1-((6-iodopyridin-3-yl)methyl)-5-(4-methoxyphenyl)pyridin-2(1*H*)-one (0.48mmol, 200mg), $PdCl_2(PPh_3)_2$ (33µmol, 23mg), CuI (24µmol, 4.5mg), $^iPr_2EtN$ (0.99mmol, 1.72µl), trimethylsilylacetylene (1.43mmol, 203µL) and DMF (3 mL, previously deoxygenated) was stirred at room temperature for 2 hours. The solvent was evaporated under reduced pressure. The residue was purified in a manifold (vac.) using a Sep-Pak silica cartridge $CH_2Cl_2$/MeOH($NH_3$)sat. 3% yielding 5-(4-methoxyphenyl)-1-((6-(2-(trimethylsilyl)ethynyl)pyridin-3-yl)methyl)pyridin-2(1*H*)-one (174mg, 93%).

*Step 4 : 1-((6-Ethynylpyridin-3-yl)methyl)-5-(4-methoxyphenyl)pyridin-2(1H)-one*

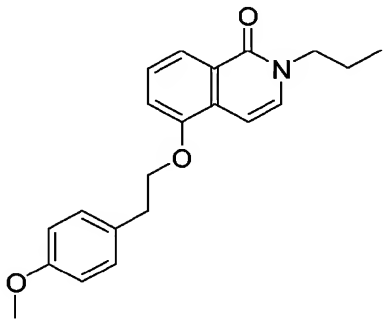
A mixture of 5-(4-methoxyphenyl)-1-((6-(2-(trimethylsilyl)ethynyl)pyridin-3-yl)methyl)pyridin-2(1*H*)-one (0.60mmol, 240mg), tetrabutylammonium fluoride (1.20mmol, 1.2mL) in THF (5mL) and $H_2O$ (1mL) was stirred at room temperature for 2 hours. The solvent was evaporated under reduced pressure. The residue was taken up in $CH_2Cl_2$, was washed with water, dried ($Na_2SO_4$) and evaporated under reduced pressure. The residue was purified in a manifold (vac.) using a Sep-Pak silica cartridge $CH_2Cl_2$/MeOH($NH_3$)sat. 3%. The fractions were collected and evaporated. The residue thus obtained was triturated with diisopropyl ether. The precipitated solid was filtered off and dried. Further purification by circular chromatography-TLC $CH_2Cl_2$/MeOH($NH_3$)sat. 3% yielding 1-((6-ethynylpyridin-3-yl)methyl)-5-(4-methoxyphenyl)pyridin-2(1*H*)-one (68mg, 35%).

M.p.: 273°C; $^1$H NMR (400 MHz, $CDCl_3$) δ8.61 (d, 1H, *J*=2.1 Hz); 7.72 (dd, 1H, *J*=8.1, 2.1 Hz); 7.60 (dd, 1H, *J*=9.4, 2.6 Hz); 7.46 (d, 1H, *J*=8.1 Hz); 7.40 (d, 1H, *J*=2.7 Hz); 7.28 (d, 2H, *J*=8.5 Hz); 6.94 (d, 2H, *J*=8.7 Hz); 6.64 (d, 2H, *J*=8.7 Hz); 7.28 (d, 2H, *J*=8.5 Hz); 6.94 (d, 2H, *J*=8,7 Hz); 6.70 (d, 1H, *J*=9.5 Hz); 5.21 (s, 2H); 3.83 (s, 3H); 3.16 (s, 1H).

*Step 5 : 1-((6-Ethylpyridin-3-yl)methyl)-5-(4-methoxyphenyl)pyridin-2(1H)-one*

According to Scheme 33 Step 3: To a suspension of Pd/C 10% (0.05 eq) in MeOH (10mL) under $N_2$ atmosphere, a solution of 1-((6-ethynylpyridin-3-yl)methyl)-5-(4-methoxyphenyl)pyridin-2(1*H*)-one (0.15mmol, 48mg) was added at room temperature. The flask was evacuated and filled with hydrogen until the pressure reached 20 psi. The resulting suspension was shaken at room temperature for 1 hour. The catalyst was filtered off and the filtrate was evaporated under vacuum to give a residue. The residue was purified in a circular chromatography-TLC $CH_2Cl_2$/MeOH($NH_3$)sat. 2% yielding 1-((6-ethylpyridin-3-yl)methyl)-5-(4-methoxyphenyl)pyridin-2(1*H*)-one (30mg, 61%). M.p.: 130°C; LC (ACE Column): RT = 3.55min; MS *m/z* (CI) $[MH]^+$= 321; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.53 (d, 1H, *J*=2.1 Hz); 7.66 (dd, 1H, *J*=8.0, 2.4 Hz); 7.58 (dd, 1H, *J*=9.5, 2.7 Hz); 7.42 (d, 1H, *J*=2.3 Hz); 7.25-7.30 (m, 2H); 7.15 (d, 1H, *J*=7.9 Hz); 6.90-6.95 (m, 2 H); 6.69 (d, 1H, *J*=9.5 Hz); 5.18 (s, 2H); 3.83 (s, 3H); 2.81 (q, 2H, *J*=7.7 Hz); 1.29 (t, 3H, *J*=7.6 Hz).

**EXAMPLE 53 : 5-(4-Methoxyphenethoxy)-2-propylisoquinolin-1(2*H*)-one (Final Compound 13-06)**



*Step 1 : 5-Chloroisoquinoline-N-oxide*

According to Scheme 34 Step 1: The title compound was prepared from isoquinolin-5-ol (1eq, 6.89mmol, 1.00g) according to the procedure described for Example 38 Step 1. The crude residue was recrystallized in $CH_2Cl_2$.to yield 5-chloroisoquinoline-N-oxide (6.58mmol, 1.06g, 96%) as a beige solid.

*Step 2 : 5-(4-Methoxyphenethoxy)isoquinoline-N-oxide*

According to Scheme 34 Step 2: The title compound was prepared from 5-chloroisoquinoline-N-oxide (1eq, 6.21mmol, 1.00g) and 1-(2-chloroethyl)-4-methoxybenzene (2eq, 12.4mmol, 2.12g) according to the procedure described for Example 1 Step 2. Reaction conditions: microwaved at 180°C for 15 min in acetonitrile.The crude product was purified by silica gel chromatography (AIT Flashsmart prepacked column 70g $SiO_2$) using cyclohexane/AcOEt 85/15 to 50/50 and MeOH to afford 5-(4-methoxyphenethoxy)isoquinoline-N-oxide (2.73mmol, 0.81g, 44%).

LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 4.98min; MS *m/z* (CI) $[MH]^+$= 296.

*Step 3 : 5-(4-Methoxyphenethoxy)isoquinolin-1(2H)-one*

According to Scheme 34 Step 3: The title compound was prepared from 5-(4-methoxyphenethoxy)isoquinoline-N-oxide (1eq, 2.73mmol, 0.81g) according to the procedure described for Example 38 Step 2. The crude product was used without being purified and yielded 5-(4-methoxyphenethoxy)isoquinolin-1(2*H*)-one (1.08mmol, 0.32g, 40%) as a brown solid.

*Step 4 : 5-(4-Methoxyphenethoxy)-2-propylisoquinolin-1(2H)-one*

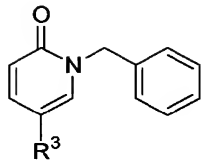
According to Scheme 34 Step 4: The title compound was prepared from 5-(4-methoxyphenethoxy)isoquinolin-1(2*H*)-one (1eq, 0.34mmol, 0.10g) and 1-bromopropyl (1.5eq, 0.51mmol, 46µL) according to the procedure described for Example 1 Step 2. Reaction conditions: microwaved at 180°C for 15 min. in acetonitrile. The crude product was purified by flash chromatography over silica gel (AIT Flashsmart prepacked column 25g $SiO_2$) using pure $CH_2Cl_2$/MeOH 100/0 to 99/1 to afford 5-(4-methoxyphenethoxy)-2-propylisoquinolin-1(2*H*)-one (59µmol, 20mg, 17%) as an orange oil.

LC (XTerra $RP_{18}$, 3.5µm, 3.0x50mm Column): RT = 4.84min; MS *m/z* (CI) $[MH]^+$= 338; $^1H$ NMR (300MHz, $CDCl_3$) δ 0.90 (t, J=7.7Hz, 3H), 1.74 (q, J=8.5Hz, 2H), 3.06 (t, J=6.6Hz, 2H), 3.73 (s, 3H), 3.89 (t, J=7.4Hz, 2H), 4.17 (t, J=6.6Hz, 2H), 6.75-6.83

(m, 3H), 6.98 (t, J=7.2Hz, 2H), 7.18 (d, J=8.2Hz, 2H), 7.29 (t, J=8.2Hz, 1H), 7.92 (d, J=8.2Hz, 1H).

The compounds in the following Tables have been synthezised according to the previous examples, as denoted in the column denoted as "Exp. Nr". The compound denoted with the asterisk has been exemplified in the Examples. When it concerns the bivalent linkers $V_1$ and $V_2$, it is noted that the left part of the linkers $V_1$ and $V_2$ is attached to the pyridinyl-moiety.

**Table 1**




| Co.nr. | Exp. nr. | $R^3$ | |
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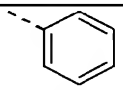
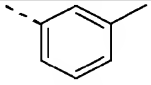
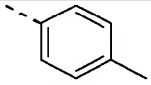
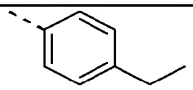
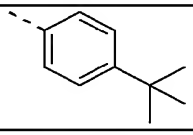
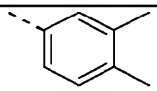
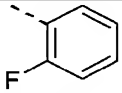
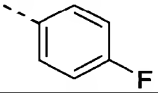
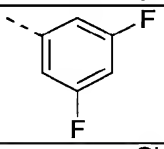
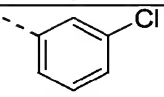
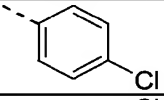
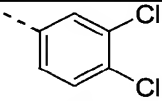
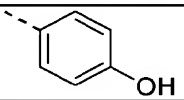
| 1-01 | 1 |  | |
| 1-02 | 2 |  | |
| 1-03 | 2 |  | |
| 1-04 | 7 |  | |
| 1-05 | 2 |  | |
| 1-06 | 2 |  | |
| 1-07 | 2 |   | |
| 1-08 | 1 |   | |
| 1-09 | 2 |   | |
| 1-10 | 2 |   | |
| 1-11 | 1 |   | |
| 1-12 | 2 |   | |
| 1-13 | 20 |   | |

| Co.nr. | Exp. nr. | $R^3$ | |
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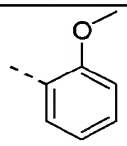
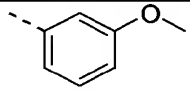
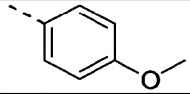
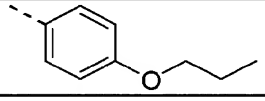
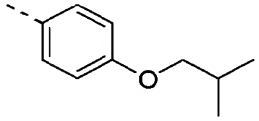
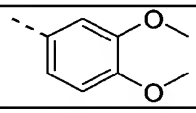
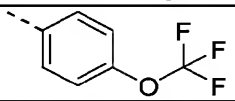
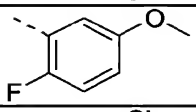
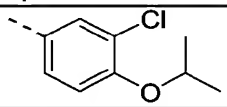
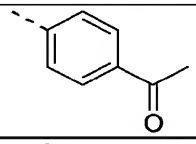
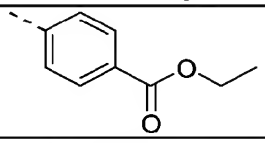
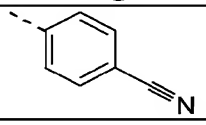
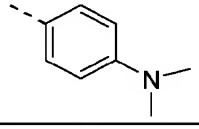
| 1-14 | 2 |  | |
| 1-15 | 2 |  | |
| 1-16 | 1 |  | |
| 1-17 | 2 |  | |
| 1-18 | 20 |  | |
| 1-19 | 2 |  | |
| 1-20 | 2 |  | |
| 1-21 | 2 |  | |
| 1-22 | 2 |  | |
| 1-23 | 2 |  | |
| 1-24 | 2 |  | |
| 1-25 | 2 |  | |
| 1-26 | 2 |  | |

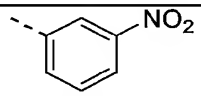
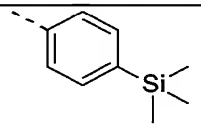
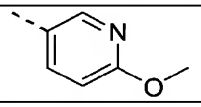
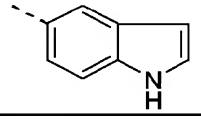
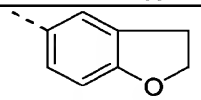
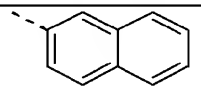
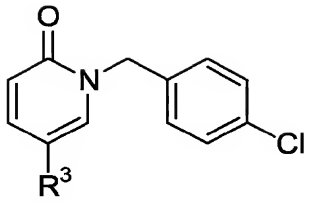
| Co.nr. | Exp. nr. | $R^3$ | |
|---|---|---|---|
| 1-27 | 2 |  | |
| 1-28 | 2 |  | |
| 1-29 | 1 |  | |
| 1-30 | 2 |  | |
| 1-31 | 2 |  | |
| 1-32 | 2 |  | |

**Table 2**




| Co.nr. | Exp. nr. | $R^3$ | |
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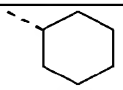
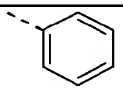
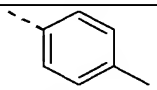
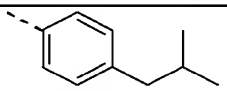
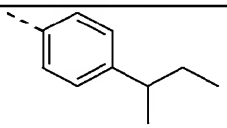
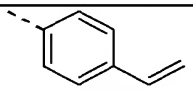
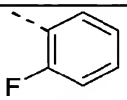
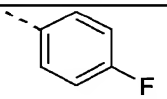
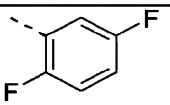
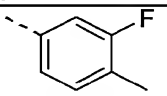
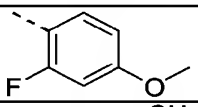
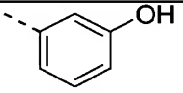
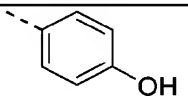
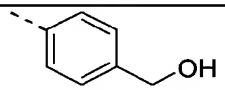
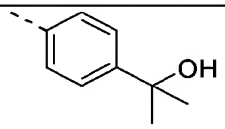
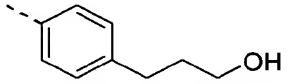
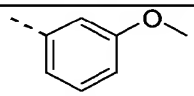
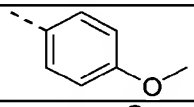
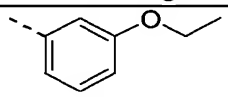
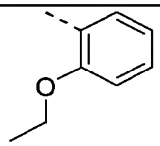
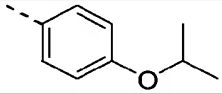
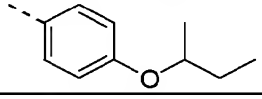
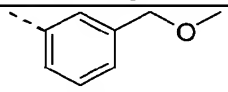
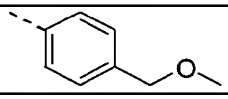
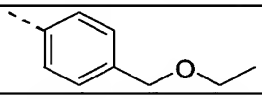
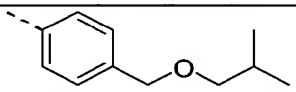
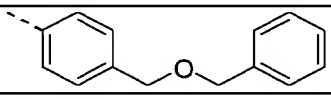
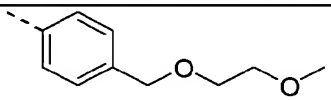
| 2-01 | 36* |  | |
| 2-02 | 2 |  | |
| 2-03 | 2 |  | |
| 2-04 | 1 |  | |
| 2-05 | 1 |  | |
| 2-06 | 1 |  | |
| 2-07 | 2 |  | |
| 2-08 | 2 |  | |
| 2-09 | 2 |  | |
| 2-10 | 2 |  | |
| 2-11 | 2 |  | |
| 2-12 | 20 |  | |
| 2-13 | 20 |  | |

| Co.nr. | Exp. nr. | $R^3$ | |
|---|---|---|---|
| **2-14** | 35 |  | |
| **2-15** | **30*** |  | |
| **2-16** | **2*** |  | |
| **2-17** | 1 |  | |
| **2-18** | 2 |  | |
| **2-19** | 1 |  | |
| **2-20** | 2 |  | |
| **2-21** | 20 |  | |
| **2-22** | 20 |  | |
| **2-23** | 2 |  | |
| **2-24** | 2 |  | |
| **2-25** | **35*** |  | |
| **2-26** | 47 |  | |
| **2-27** | 35 |  | |
| **2-28** | 47 |  | |